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Family Functioning as a Moderator of Neurocognitive Outcome Among Survivors of Pediatric Acute Lymphoblastic Leukemia

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Family Functioning as a Moderator of Neurocognitive Outcomes Among Survivors of Pediatric Acute Lymphoblastic Leukemia

by

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Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas at Austin

August 2016

Dedication

This project is dedicated to the patients and families of the Children's Blood and Cancer Center at Dell Children's Medical Center, who inspired this project and generously donated their time to make it a reality.

Acknowledgements

There are many people who I would like to thank for their assistance during the completion of this dissertation. First, I would like to thank my co-supervisors, Dr. Kevin Stark and Dr. Emily Greenspahn, for their guidance and support throughout this process. I would also like to thank my committee members, Dr. Timothy Keith, Dr. Greg Allen, Dr. Barbara Jones, and Dr. Puja Patel, for sharing their time and expertise. In addition, I would like to thank Dr. Greenspahn and Dr. Patel for being wonderful supervisors and mentors to me during my time at the CBCC.

I am also thankful for and would like to acknowledge many others who have helped me along the way: my family, for always believing in me and encouraging me; the Knotty Knitters, for keeping me sane throughout graduate school; my fellow students at the University of Texas, for making graduate school fun; and my fellow interns at the Kennedy Krieger Institute, for the study dates and coffee shop sessions that helped me cross the finish line. I am also grateful to the CRCST research team and the staff of the CBCC for their assistance with the completion of this project. In particular, thank you to Kris Scardamalia for going above and beyond to help me with this study.

Finally, I would like to thank my moms, Deborah and Linda, my father Mick and stepmother Terri, and my partner, Brad, for their unending love and support. I could not have done this without you and I cannot thank you enough for all you have done for me.

Family Functioning as a Moderator of Neurocognitive Outcomes Among Survivors of Pediatric Acute Lymphoblastic Leukemia

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The University of Texas at Austin, 2016

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Chemotherapy treatment for pediatric Acute Lymphoblastic Leukemia (ALL) can affect neurocognitive functioning across many areas, including attention and executive functioning. Some variables that may moderate or protect against neurocognitive deficits following chemotherapy treatment have been identified, including gender, age at diagnosis, time since treatment, and socioeconomic status. Evidence from pediatric traumatic brain injury and pediatric brain tumor populations suggests that positive family functioning serves as a protective factor for neurocognitive outcomes of children who survive these conditions. However, no research was found that examines whether positive family functioning similarly moderates the effects of chemotherapy on the neurocognitive functioning of survivors of pediatric ALL. The purpose of this study was to examine the effect of family functioning upon neurocognitive outcome among survivors of pediatric ALL treated with chemotherapy, specifically in the domains of attention and executive functioning.

Participants were 20 children and adolescents who completed chemotherapy-only treatment for ALL and 20 healthy comparison participants, all within the ages of 8 and 15. Participants were administered measures of attention and executive functioning. In addition, one caregiver for each child completed a measure of family functioning and

rating forms of their child's attention and executive functioning. Multiple regression analyses were conducted to examine the relationship between family functioning and neurocognitive functioning.

Tests of the interaction between family functioning and group membership in accounting for variance in neurocognitive functioning indicated that family functioning did not have a differential effect on neurocognitive functioning for the survivors as compared to the healthy children. Family functioning accounted for a significant amount of variance in caregiver ratings of attention and executive functioning for all participants, even after controlling for demographic variables in the sample as a whole and demographic and treatment related variables in the clinical group. That is, caregivers who rated their family as having more difficulties with family functioning also rated their child as having more difficulties with attention and executive functioning. Additionally, survivors performed significantly worse than healthy controls on measures of sustained attention, working memory, and processing speed, providing additional evidence that this population is at risk for neurocognitive late effects in these areas.

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Chapter 1: Introduction

A diagnosis of cancer in a child is perhaps one of the most difficult situations a family can experience. It is estimated that more than 15,000 youth ages 0-19 are diagnosed with cancer each year in the United States alone (American Cancer Society [ACS], 2014). Worldwide, almost 1 out of every 285 children are diagnosed with cancer before the age of 20 and roughly 1 out of every 530 young adults between the ages of 20 and 39 is a survivor of childhood cancer (Ward, DeSantis, Robbins, Kohler, & Jemal, 2014). The most common form of cancer among children and adolescents is Acute Lymphoblastic Leukemia (ALL), which accounts for nearly 30% of childhood cancers (Ward et al., 2014). ALL occurs across all ethnic groups and in both genders, but is slightly more prevalent among Hispanic and Caucasian children and male children (Hunger & Mullighan, 2015). It is most often diagnosed in children between ages 3 through 5 (Hunger & Mullighan, 2015).

ALL occurs when stem cells develop into a type of white blood cell known as lymphocytes or leukemic cells (Bisen-Hersh, Hineline, & Walker, 2011). These cells, unlike typical white blood cells, are unable to fight infection and their proliferation leaves less room for the formation of healthy blood cells and platelets (Bisen-Hersh et al., 2011). Lymphocytes originate in bone marrow but can be carried through the bloodstream to nearly every organ system in the body, including the Central Nervous System (CNS; Bisen-Hersh et al., 2011; Mulhern & Butler, 2006). Although some potential genetic, environmental, and viral contributions to the development of ALL have been identified, the exact cause of the majority of cases of ALL is unknown (Bisen-Hersh et al., 2011; Hunger & Mullighan, 2015).

Diagnosis of ALL is most commonly made through a bone marrow aspiration (Mulhern & Butler, 2006). Once diagnosed, the child with ALL is classified into one of four categories (low-risk, standard-risk, high-risk, and very high-risk) based upon the degree of progression of lymphocytes beyond the bone marrow and blood into other organ systems in the body (Riccio, Sullivan, & Cohen, 2010). This classification helps to determine the type and degree of treatment that the child receives. Due to improvements in treatment regimens over the past forty years, approximately 90% of children diagnosed with ALL now survive (Hunger & Mullighan, 2015). This decrease in mortality rates is largely attributed to the introduction of prophylactic CNS treatment, which prevents the spread of leukemia into the CNS and thus prevents the occurrence of CNS relapse, one of the leading causes of death in ALL (Buizer, de Sonneville, & Veerman, 2009).

The first form of CNS prophylaxis was cranial irradiation or cranial radiation therapy (CRT; Buizer et al., 2009). While CRT greatly improved survival rates in ALL, it was also found to contribute to the development of long-term and progressive impairments in cognitive functioning (Montour-Proulx et al., 2005). These deficits in intellectual, academic, and neuropsychological functioning caused by CNS prophylactic treatment came to be known as "neurocognitive late effects" and pediatric oncologists sought ways to decrease the occurrence of such deficits while still ensuring survival (Daly et al., 2008; Espy et al., 2001). This led to the development of treatment protocols consisting of intrathecal chemotherapy, which is administered directly into the spinal fluid via a lumbar puncture (Brown et al., 1998; Buizer et al., 2009; Mulhern & Palmer, 2003). Currently, chemotherapy-only treatment protocols are utilized for majority of patients with ALL (Kingma et al., 2002; Espy et al., 2001; Moleski, 2000).

While the use of chemotherapy-only instead of radiation therapy has helped to decrease the neurocognitive late effects experienced by survivors of ALL, research has

found that chemotherapy-only treatment can still cause subtle neurocognitive late effects (Anderson & Kunin-Batson, 2009; Iyer, Balsamo, Bracken, & Kadan-Lottick, 2015). Survivors of pediatric ALL treated with only chemotherapy have been shown to experience declines in intellectual and academic functioning following treatment (Moleski, 2000; Mulhern & Palmer, 2003; Iyer et al., 2015; Peterson et al., 2008). These declines in intellectual and academic functioning are thought to be secondary to deficits in core neuropsychological domains (Butler & Haser, 2006; Moleski, 2000; Mulhern & Palmer, 2003).

The specific neuropsychological domains most often found to be impaired among survivors of pediatric ALL treated according to chemotherapy-only protocols are attention and executive functioning (Anderson & Kunin-Batson, 2009; Bisen-Hersh et al., 2011; Buizer et al., 2009; Campbell et al., 2007; Peterson et al., 2008; Riccio et al., 2010; Schatz, Kramer, Ablin, & Matthay, 2000; Winick, 2011). Among this population, deficits in attention have been found across the subdomains of selective attention, divided attention, sustained attention, and shifting attention (Ashford et al., 2010; Baron, 2004; Buizer, de Sonneville, van den Heuvel-Eibrink, & Veerman, 2005; Carey et al., 2008; Harila, Winqvist, Lanning, Bloigu, & Harila-Saari, 2009; Kingma et al., 2002; Lesnik, Ciesielski, Hart, Benzel, & Sanders, 1998; Reddick et al., 2006). Subdomains of executive functioning that have found to be impaired among this population include cognitive flexibility/working memory, goal setting/planning, information processing/processing speed, and attentional control/inhibition (Ashford et al., 2010; Carey et al., 2008; Harila et al., 2009; Jansen, 2008; Kingma et al., 2002; Lesnik et al., 1998; Waber et al., 1995). While these weaknesses in attention and executive functioning may be less pronounced than the weaknesses observed among survivors of ALL treated with radiation therapy, they still have important consequences for the survivors' lives

after cancer (Anderson & Kunin-Batson, 2009). Neurocognitive late effects among this population have been found to be associated with difficulties in social, emotional, and behavioral functioning; concerns about school performance; and lower levels of quality of life than healthy population norms (Kanellopoulos, Hamre, Dahl, Fossa, & Ruud, 2013; Kunin-Batson, Kadan-Lottick, & Neglia, 2014; Iyer et al., 2015; Moyer et al., 2012; Patel, Wong, Cuevas, & Van Horn, 2013).

As researchers gain a better understanding of the neurocognitive late effects associated with chemotherapy-only protocols for the treatment of childhood ALL, emphasis in research is now shifting towards the identification of variables that may serve to moderate or protect against the development of neurocognitive late effects (Daly et al., 2008; Mulhern & Palmer, 2003). Moderators and mediators have been identified for medical, treatment-related, child-related, and demographic factors, such as disease classification, treatment intensity, age at diagnosis, gender, and socioeconomic status (Brouwers, 2005; Buizer et al., 2005; Buizer et al., 2009; Moleski, 2000; Mulhern & Palmer, 2003; Peterson et al., 2008; Stehbens et al., 1994; Waber et al., 2012; Winick, 2011). In addition, some researchers have suggested that psychosocial variables such as family functioning may moderate neurocognitive outcome among survivors of pediatric ALL, as there is evidence from the literature on pediatric traumatic brain injury and pediatric brain tumors that the level of functioning in a family influences how well a child or adolescent recovers from neurocognitive insult (Anderson & Kunin-Batson, 2009; Max et al., 1999; Nadebaum, Anderson, & Catroppa, 2007; Taylor et al., 1999; Yeates et al., 1997).

Family functioning refers to the extent to which a family is able to engage in the interactional patterns necessary for the achievement of family goals (Walsh, 2011). A model of family functioning that has been used in research with the pediatric cancer

population is the McMaster Model of Family Functioning (MMFF; Carlson, 2003; Epstein, Ryan, Bishop, Miller, & Keitner, 2003). The MMFF consists of six dimensions (problem solving, communication, role functioning, affective responsiveness, affective involvement, and behavior control) that are thought to be important for the health of the members of the family and the successful achievement of family tasks (Epstein et al., 2003; Lebow & Stroud, 2011). Within each dimension, researchers have identified behaviors and interaction patterns that range from "most ineffective" to "most effective" (Epstein et al., 2003). Those deemed "most ineffective" tend to lead to the development of clinically significant difficulties for the family, while those deemed "most effective" lead to physical and emotional health for the members of the family (Epstein et al., 2003). Families of survivors of pediatric ALL have been found to demonstrate lower rates of functioning across the dimensions of the MMFF (Alderfer, Navsaria, & Kazak, 2009).

Evidence from the pediatric traumatic brain injury and pediatric brain tumor populations suggests that positive family functioning serves as a protective factor for neurocognitive outcomes of children who survive these conditions. In the field of traumatic brain injury, research suggests that the level of functioning in a family influences how well a child or adolescent within that family recovers from neurocognitive insult (Max et al., 1999; Nadebaum et al., 2007; Taylor et al., 1999; Yeates et al., 1997). Two studies have investigated this phenomenon among survivors of pediatric brain tumors and found similar results (Ach et al., 2013; Carlson-Green, Morris, & Krawiecki, 1995). However, no known research has examined whether positive family functioning similarly moderates the effects of CNS-directed chemotherapy on the neurocognitive functioning of survivors of pediatric ALL.

The purpose of this study was to investigate whether family functioning moderates neurocognitive functioning following chemotherapy treatment for ALL. Based

upon a multidimensional model of attention and Anderson's model of executive function (EF), four subcomponents of attention and four subcomponents of EF were examined (Anderson, 2002). The attention subcomponents were: selective, divided, sustained, and shifting. The EF subcomponents were: cognitive flexibility (working memory), goal setting (planning), attentional control (inhibition), and information processing (processing speed). Caregiver ratings of survivors' attentional and executive functioning were examined as well. It was hypothesized that survivors of ALL from poorer functioning families would experience more severe neurocognitive late effects than those from higher functioning families. Moreover, it was hypothesized that such a relationship between family functioning and neurocognitive functioning would not be found among healthy control children.

Chapter 2: Literature Review

Acute Lymphoblastic Leukemia

Prevalence.

Childhood cancer, although relatively rare, is more common than many people realize and is a significant health problem around the world (Moore, 2005; Riccio et al., 2010). Approximately 1 out of every 300 children under the age of 16 has a diagnosis of cancer (Riccio et al., 2010). On average, one to two out of every 10,000 children is diagnosed with cancer each year in the United States (Butler & Haser, 2006; Moore, 2005). Cancer is the leading cause of death by disease among children under the age of 15 and the second leading cause of death among children and adolescents overall, with accidents being the first leading cause (American Cancer Society, 2015). In 2015 alone, approximately 10,380 children under the age of 15 were expected to be diagnosed with cancer in the United States and 1,250 cancer deaths were expected to occur among that age group in that year (American Cancer Society, 2015).

The incidence of childhood cancer varies by age and by type of cancer, with some cancers more common at certain ages than others (Riccio et al., 2010). In general, the types of cancer most often seen in children are quite different from those common among adults (Riccio et al., 2010). Types of cancer commonly seen in children and adolescents are "leukemias, brain and other nervous system tumors, lymphomas (lymph node cancers), bone cancers, soft tissue sarcomas, kidney cancers, eye cancers, and adrenal gland cancers (ACS, 2006)" (Riccio et al., 2010, p. 207), with leukemias and solid tumors most prevalent in this age group (Riccio et al., 2010).

Leukemias are the most common form of cancer among children and adolescents, accounting for approximately one-third of cancers in children under the age of 15 and

one-fourth of cancers in people under the age of 20 (Bisen-Hersh et al., 2011; Butler & Haser, 2006; Riccio et al., 2010). Leukemia refers to a diverse set of diseases of the blood forming tissues (Brown et al., 1992; Daly et al., 2008; Riccio et al., 2010). Leukemia is characterized by the production of large amounts of abnormal early-stage white blood cells called leukocytes (Daly et al., 2008; Riccio et al., 2010). The leukocytes block production of normal white blood cells and therefore impede the child's ability to fight off infection (Daly et al., 2008; Riccio et al., 2010). There are two types of normal white blood cells in which leukemia may develop: lymphoid cells and myeloid cells (U.S. Department of Health and Human Services, 2008). Leukemias that begin in lymphoid cells are referred to as lymphocytic, or lymphoblastic, leukemias; leukemias that begin in myeloid cells are referred to as myelogenous, or myeloblastic, leukemias (U.S. Department of Health and Human Services, 2008). Leukemia can also be classified as either acute or chronic, depending on the speed with which the disease develops and progresses (U.S. Department of Health and Human Services, 2008). Acute leukemias are those that progress quickly, whereas chronic leukemias progress more slowly (U.S. Department of Health and Human Services, 2008). Altogether, then, there are four main types of leukemia: acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, and chronic myelogenous leukemia (Riccio et al., 2010; U.S. Department of Health and Human Services, 2008).

The most common form of leukemia among children is acute lymphocytic leukemia (ALL), which is also known as acute lymphoblastic leukemia (Butler & Haser, 2006). ALL is the most common cancer among children and adolescents ages 1 to 16 and accounts for approximately 76% of all cases of pediatric leukemia (Leukemia & Lymphoma Society, 2014). Of the approximately 6,000 cases of ALL diagnosed annually in the United States, roughly 76% percent of these are among children, adolescents, and

young adults less than 20 years of age (American Cancer Society, 2015). ALL occurs across ethnic groups but is slightly more prevalent among Caucasian and Hispanic children than among African American or Asian American children (Hunger & Mullighan, 2015). The yearly incidence of ALL among white children is about 3 or 4 per 100,000 (Mennes et al., 2005; Mulhern & Palmer, 2003). It is more common among boys than girls, with 1.3 males diagnosed for every 1 female diagnosed (McNeil, Cote, Clegg, & Mauer, 2002; Mulhern & Butler, 2006). The majority of cases of ALL are diagnosed in children between the ages of 3 to 5 years (Hunger & Mullighan, 2015).

Characteristics of ALL.

ALL is a "malignant disorder of lymphoid cells" that "results when a surplus of stem cells develop into lymphocytes, a type of white blood cell also referred to as leukemic cells" (Bisen-Hersh et al., 2011, p. 293). Lymphocytes are unable to fight infection and the proliferation of them leaves less room for healthy blood cells and platelets to form (Bisen-Hersh et al., 2011). The lymphocytes are originally found in the bone marrow (Mulhern & Butler, 2006). From there they enter the bloodstream and are transported, via the circulatory system, to nearly every organ system in the body (Bisen-Hersh et al., 2011; Mulhern & Butler, 2006). This includes the central nervous system (CNS), which consists of the brain and the spinal cord (Carlson, 2010). Possible genetic, environmental, and viral influences on the development of ALL have been identified (Bisen-Hersh et al., 2011; Mulhern & Butler, 2006). For example, children with the genetic disorder Down syndrome have been found to be at an increased risk for the development of leukemia (Riccio et al., 2010). However, the genetic and environmental influences that have been identified as implicated in the development of ALL so far do

not account for the majority of cases of the disease and the exact causes of most cases of ALL remain unknown (Bisen-Hersh et al., 2011; Daly et al., 2008; Riccio et al., 2010).

Presenting symptoms of ALL can include fever, fatigue, paleness of the skin, bone pain, easy bleeding or bruising, infection, swelling of the abdomen, swollen lymph nodes, enlargement of the thymus gland, headache, seizures, vomiting, rashes, gum problems, and/or weakness (Mulhern & Butler, 2006; Riccio et al., 2010). Since many of these symptoms resemble those of a number of nonmalignant conditions, definitive diagnosis is based upon a combination of laboratory tests and imaging results and is sometimes delayed (Mulhern & Butler, 2006; Riccio et al., 2010). The specific laboratory tests used to diagnosis ALL include blood smear, bone marrow aspiration, bone marrow biopsy, spinal tap, and lymph node biopsy, with bone marrow aspiration being the most commonly used diagnostic test for this condition (Mulhern & Butler, 2006; Riccio et al., 2010). Once a child is diagnosed with ALL they are classified into one of four categories based upon the progression of the disease: low-risk, standard-risk, high-risk, and very high-risk (Riccio et al., 2010). This classification is made based upon the presence of cancer cells beyond the bone marrow and blood, in organs such as the liver, spleen, or lymph nodes (Riccio et al., 2010).

Treatment for ALL.

Treatment for ALL generally lasts for two to three years and consists of multiple phases (Bisen-Hersh et al., 2011; Butler & Haser, 2006; Moleski, 2000). Prior to the early 1960s, survival rates for ALL were very low (Moleski, 2000; Moore, 2005). However, survival rates have improved dramatically since that time due to marked improvements in the treatment (Butler & Haser, 2006; Winick, 2011). The factor most commonly credited as responsible for decreased mortality rates of ALL over the past several decades has

been the introduction of prophylactic CNS treatment, which prevents leukemia from spreading into the CNS (Buizer et al., 2009; Hill, Ciesielski, Sethre-Hofstad, Duncan, & Lorenzi, 1997; Von der Weid et al., 2003). CNS prophylaxis is necessary because the blood-brain barrier prevents chemotherapeutic agents delivered to the rest of the body from reaching the CNS (Buizer et al., 2009; Moleski, 2000). Without CNS prophylaxis the CNS is a sanctuary for leukemic cells and the chance of CNS relapse is high (Butler & Haser, 2006; Mennes et al., 2005; Mulhern & Palmer, 2003). CNS relapse, also known as CNS leukemia, occurs when leukemic cells invade and proliferate within the CNS (Brown et al., 1992; Moleski, 2000). Without CNS prophylaxis up to 80% of children and adolescents with ALL experience CNS relapse (Buizer et al., 2009). CNS relapse is a major cause of mortality in ALL (Buizer et al., 2009). The best way to treat CNS relapse is to prevent it from occurring, so CNS prophylaxis has become a standard part of treatment for children with ALL (Brown et al., 1992; Iuvone et al., 2002).

These new treatment protocols have served to nearly eliminate the occurrence of CNS relapse, which now occurs in less than 10% of cases of ALL (Buizer et al., 2009; Moleski, 2000). Currently, approximately 90% of children and adolescents ages 0-19 years diagnosed with ALL reach long-term event-free survivorship (American Cancer Society, 2014; Hunger & Mullighan, 2015). As of January 1, 2010, there were 60,489 survivors of childhood ALL living in the United States (American Cancer Society, 2014).

Late effects of treatment.

With the increased survival rates that have accompanied improvements in the treatment of childhood ALL in the past several decades, interest has grown in the study of the "late effects" of CNS prophylactic treatment (Bisen-Hersh et al., 2011; Brouwers, 2005). Late effects are impairments in functioning that occur after the successful

completion of cancer therapy (Mulhern & Butler, 2006). They are generally defined as occurring two or more years after the time of diagnosis and are thus different from "acute effects", the "effects of disease and treatment that are acute or subacute and time limited, such as chemotherapy-induced nausea and vomiting or temporary cognitive changes induced by cancer therapy" (Mulhern & Butler, 2006, p. 262). Late effects are generally considered to be chronic and progressive (Mulhern & Butler, 2006).

Among survivors of childhood cancer overall, approximately two-thirds experience at least one long-term consequence, or late effect, from their cancer and its treatment (Nathan et al., 2007). Survivors of childhood ALL are especially at risk for long-term and progressive impairment in the area of cognitive functioning because CNS prophylaxis treatment can be toxic to the developing brain (Kesler et al., 2010; Nathan et al., 2007). The intellectual, academic, and neuropsychological deficits caused by CNS prophylactic treatment are known collectively as "neurocognitive late effects" (Daly et al., 2008; Espy et al., 2001).

The first form of CNS prophylactic treatment for ALL, introduced in the late 1960s and early 1970s, was cranial irradiation or cranial radiation therapy (CRT; Buizer et al., 2009; Montour-Proulx et al., 2005). At first, CRT consisted of 24 Gy of radiation delivered to the spinal cord (Buizer et al., 2009; Von der Weid et al., 2003). Although it served to significantly decrease the incidence of CNS relapse, and thus increased survival rates among children with ALL, research found a high incidence of neurocognitive deficits among survivors of ALL treated with CRT (Brown et al., 1992; Montour-Proulx et al., 2005). These included significant declines in overall intellectual functioning as well as impairments in short-term memory, attention, information processing, motor speed, and perception (Brown et al., 1992; Moleski, 2000). Furthermore, survivors of ALL treated with CRT were found to have an increased incidence of special education

placements for learning disabilities and to have decreased rates of secondary school completion (Mennes et al., 2005).

Based upon this research into the late effects of CRT, pediatric oncologists began to explore ways to decrease the amount of CRT administered to children with ALL, while still ensuring survival. They began reducing the dosage of CRT (to 18 or even 12 Gy) and adding chemotherapy to the treatment protocols for childhood ALL (Buizer et al., 2009; Montour-Proulx et al., 2005). The chemotherapy was delivered intrathecally (directly into the spinal fluid) and typically consisted of the drug methotrexate (MTX), alone or in combination with other drugs (Brown et al., 1998; Buizer et al., 2009; Mulhern & Palmer, 2003). It was found that the level of radiation could be reduced without negatively impacting CNS relapse-free survival rates, and a combination of CRT and intrathecal (IT) chemotherapy was the primary form of CNS prophylaxis for childhood ALL in the 1970s and early 1980s (Buizer et al., 2009; Kingma et al., 2002; Von der Weid et al., 2003). However, a high incidence of neurocognitive late effects persisted among survivors treated with combined modality (chemotherapy plus CRT) therapy, despite the decreased levels of radiation that were involved (Buizer et al., 2009; Kingma et al., 2002; Montour-Proulx et al., 2005).

In the mid-1980s, CRT was eliminated and chemotherapy-only treatment protocols began to be used as CNS prophylaxis for non-high-risk childhood ALL (Hill et al., 1997; Jansen et al., 2008; Kingma et al., 2002). It was found that similar, or even better, survival rates could be generated with chemotherapy-only treatment among children with standard-risk ALL (Buizer et al., 2005; Moleski, 2000; Von der Weid et al., 2003). Currently, CRT is only used with a small percentage of children who are deemed to be at the highest risk for CNS relapse (American Cancer Society, 2014; Hunger & Mullighan, 2015). Typical CNS prophylaxis for non-high risk ALL now consists of

systemic and IT chemotherapy (Iyer et al., 2015; Montour-Proulx et al., 2005). The specific chemotherapeutic agents used vary across medical institutions, but IT chemotherapy typically consists of MTX, alone or in combination with other drugs such as cytosine arabinoside (bytarabine), anthracyclines (such as doxorubicin), asparaginase, mercapclines, vincristine, and corticosteroids (Bisen-Hersh et al., 2011; Moleski, 2000).

Neurocognitive Late Effects of Chemotherapy

Given that chemotherapy-only protocols are now the standard form of CNS prophylaxis for the majority of children and adolescents with ALL, research interest in the potential neurocognitive late effects of this form of treatment has grown immensely over the past few decades (Buizer et al., 2009; Butler & Haser, 2006; Iyer et al., 2015). Although there has been some inconsistency among the results of studies in this area, methodologically sound studies on the intellectual, academic, and neuropsychological functioning of ALL survivors treated with chemotherapy for CNS prophylaxis have shown that a significant amount of survivors show evidence of deficits in at least one area of functioning (Moleski, 2000; Iyer et al., 2015; Peterson et al., 2008; van der Plas et al., 2015).

Intellectual functioning.

In terms of intellectual functioning, studies have found that survivors of childhood ALL treated with chemotherapy demonstrate impaired performance on measures of Full Scale IQ (FSIQ; Giralt et al., 1992; Hill et al., 1997; Raymond-Speden, Tripp, Lawrence, & Holdaway, 2000), Verbal IQ (VIQ; Giralt et al., 1992; Harila et al., 2009; Hill et al., 1997; Kingma et al., 2002; Raymond-Speden et al., 2000), Performance IQ (PIQ; Brown et al., 1998; Giralt et al., 1992; Harila et al., 2009; Hill et al., 1997; Raymond-Speden et al., 2000), and Simultaneous Processing (Brown et al., 1992). Furthermore, some studies

have found that children and adolescents receiving chemotherapy for CNS prophylaxis in ALL show evidence of declines in various areas of intellectual functioning over time after their treatment has ended. These areas include FSIQ (Mulhern, Fairclough, & Ochs, 1991; Ochs et al., 1991), VIQ (Harila et al., 2009; Mulhern et al., 1991; Ochs et al., 1991), and PIQ (Jansen et al., 2006; Montour-Proulx et al., 2005; Mulhern et al., 1991). However, other studies have found ALL survivors treated with chemotherapy-only to perform similarly to controls on measures of intellectual functioning (Anderson, Godber, Smibert, Weiskop, & Ekert, 2000; Ashford et al., 2010; Kingma et al., 2001; Rowland et al., 1984; Stehbens et al., 1994; Tamaroff et al., 1982; Ueberall et al., 1996; Von der Weid et al., 2003; Waber et al., 1995). Other studies found deficits in intellectual functioning relative to controls that approached, but did not reach, statistical significance (Carey et al., 2008; Kaemingk, Carey, Moore, Herzer, & Hutter, 2004; Reddick et al, 2006; Schatz et al., 2000).

In order to resolve these contradictions as to the presence or absence of deficits in intellectual functioning among ALL survivors treated with chemotherapy-only protocols, Moleski conducted an extensive review of the literature in 2000. Reviewing 33 studies published between 1981 and 1997, Moleski found that roughly two-thirds of the studies reported deficits in at least one area of intellectual functioning. Many of the studies that did not report finding evidence of impaired intellectual functioning among this population had significant methodological weaknesses (Moleski, 2000). In some of the studies, researchers reported that chemotherapy alone was not neurotoxic because the patients' mean IQ was in the average range. However, this conclusion is problematic because research has found that healthy siblings of ALL survivors tend to function in the above average range of intellectual functioning, with an average IQ value of approximately 112 to 113 (Moleski, 2000). Therefore, it is reasonable to assume that the

survivors themselves may have been functioning in the above average range as well if not for their treatment, and IQ scores in the lower end of the average range may in fact represent a decline in functioning for this population. Because of this, scholars have argued that is important to use matched controls, as opposed to normative data, for comparison when investigating neurocognitive late effects in this population (Moleski, 2000).

Some studies included in Moleski's seminal review of the literature enlisted a non-CNS treated cancer group in order to control for school absences due to treatment as well as for the psychological experience of having cancer (Moleski, 2000). All but one of these studies found evidence of impaired intellectual functioning among ALL patients receiving IT chemotherapy for CNS prophylaxis. Other studies used a healthy non-sibling control group for comparative purposes (Moleski, 2000). Two of these studies did not find evidence of declines in intellectual functioning among the subjects who had received chemotherapy. However, these two articles, which report on results from the same larger study, included both CNS- and non-CNS-treated cancer patients in their "chemotherapy-only" group. Therefore, no conclusions about the effects of chemotherapy used for CNS prophylaxis can be made, as the CNS-treated subjects were mixed with what should have been a non-CNS cancer control group. Another study that reported finding no evidence of declines in intellectual functioning among ALL survivors treated with chemotherapy had only 3 such subjects in its study (Moleski, 2000), a sample size that makes rendering conclusions for the larger population rather difficult. Overall, Moleski found that studies which had included a control group of either siblings or non-CNS-treated cancer patients consistently found significant differences in intellectual functioning between the control groups and ALL survivors treated with chemotherapy.

Peterson and colleagues followed up Moleski's review of the literature with a meta-analysis in 2008. Criteria used for inclusion in the meta-analysis were: inclusion of participants who had competed chemotherapy-only treatment for pediatric ALL as well as a comparison group that did not receive CNS-directed treatment, publication in English, inclusion of enough original data to allow for calculation of effect sizes, and publication after 1990 (Peterson et al., 2008). Of the 160 relevant articles originally found, the majority failed to meet criteria for inclusion in the study and only 13 were included in the meta-analysis. The results of the analysis indicated that survivors of pediatric ALL treated with chemotherapy alone had significantly lower FSIQ scores as compared to control groups (Mean effect size = 0.55, 95% Confidence Interval = 0.27 – 0.83, n = 10). After eliminating from analysis the three studies that had used test norms as the control group and the three that utilized foreign translations of intelligence tests, the recalculated mean effect size for FSIQ from the remaining seven studies was still significantly different from zero (M = 0.76, 95% CI = 0.42 – 1.12, n = 7). Similar results were found for the index scores VIQ and PIQ and for subtests measuring working memory and processing speed as well. These results provide empirical support to the assertion that survivors of pediatric ALL treated according to chemotherapy-only protocols do experience deficits in intellectual functioning following their treatment.

A more recent meta-analysis conducted by Iyer and colleagues confirmed the findings of these earlier reviews through examination of ten studies meeting more stringent inclusion criteria (age < 21 years at time of ALL diagnosis, ≥ 5 years postdiagnosis or ≥ 2 years off treatment and in continuous first remission, no history of CRT, cancer-free at the time of assessment, and comparison with a healthy control group (Iyer et al., 2015). 8 of the 10 studies included in the analysis assessed intellectual functioning. For FSIQ, 432 pediatric ALL survivors were compared with 465 healthy

control subjects. For VIQ and PIQ, 452 ALL survivors met criteria for inclusion and were compared with 510 healthy control subjects. In regards to FSIQ, the ALL survivor group performed 0.52 standard deviations lower than the healthy control group, which equated to approximately 7.8 IQ points and was a statistically significant difference (95% CI = -0.68 to -0.37, $p < .001$). For VIQ, the survivor group performed 0.54 standard deviations lower than the healthy control group, equating to 8.1 IQ points and representing a statistically significant difference (95% CI = -0.69 to -0.40, $p < .001$). Significant differences were also found for PIQ, with the survivor group performing 0.41 standard deviations lower than the control group (6.15 IQ points, 95% CI = -0.56 to -0.27, $p < .001$). In sum, results of this meta-analysis indicated that survivors of pediatric ALL performed significantly worse than healthy peers on measures of FSIQ, VIQ, and PIQ.

Neuropsychological functioning.

Deficits in intellectual and academic functioning among this population have been well established in much of the literature (Mulhern & Palmer, 2003). Originally, it was thought that these deficits could be due to the general effects of chronic illness and school absenteeism (Mulhern & Palmer, 2003). However, studies involving control groups comprised of pediatric cancer patients whose treatment did not include CNS directed chemotherapy have disproved this notion (Mulhern & Palmer, 2003). It is now believed that deficits in intellectual and academic functioning are "secondary" late effects resulting from deficits in what are called "core" areas of neuropsychological functioning, such as attention, working memory, processing speed, and memory (Bisen-Hersh et al., 2011; Schatz et al., 2000). It is thought that these deficits in core mental processes impair the development of higher-level abilities, leading to the declines in IQ level found among this population (Bisen-Hersh et al., 2011; Schatz et al., 2000). Research has shown that

decreases in Verbal, Performance, and Full Scale IQ scores among this population are largely the result of domain specific weaknesses in processing speed and working memory (Kahalley et al., 2013; Patel et al., 2013).

The focus of research on neurocognitive late effects of chemotherapy among survivors of childhood ALL has shifted from the study of global intellectual functioning to the identification of patterns of specific neuropsychological deficits in this population (Butler & Haser, 2006; Moleski, 2000; Mulhern & Palmer, 2003). Evidence from these studies has shown that survivors of childhood ALL treated with chemotherapy alone consistently show declines in at least one area of "core" neuropsychological functioning (Moleski, 2000). The specific core neuropsychological domains most commonly affected in this population are attention and executive functioning (Anderson & Kunin-Batson, 2009; Buizer et al., 2009; Peterson et al., 2008). These basic neuropsychological processes are crucial for the acquisition of new information and skills, and deficits in these areas are thought to underlie poor performance of ALL survivors in the classroom and beyond (Buizer et al., 2009; Mulhern & Palmer, 2003).

Attention.

The domain of attention consists of a number of subdomains, including selective attention, divided attention, sustained attention, and shifting attention (Baron, 2004; Ginstfeldt & Emanuelson, 2010; Mirsky, Anthony, Duncan, Ahearn, & Kellam, 1991). Selective attention is the ability to maintain focus on a particular cognitive set or stimuli "in the presence of background 'noise' or distraction" (Baron, 2004, p. 222). Commonly used tests of selective attention include digit span tasks, where participants are asked to repeat a sequence of numbers read to them by the examiner. Divided attention is the ability to "respond to more than one task or event simultaneously" (Baron, 2004, p. 222).

Commonly administered tests of divided attention include trail making tests, in which the participant has to draw a line between circles while alternating between numbers and letters in sequence. Sustained attention is defined as the "ability to maintain vigilance and respond consistently during continuous or repetitive activity" (Baron, 2004, p. 223). Commonly administered tests of sustained attention include continuous performance tests, which require the subject to attend to a visual or auditory presentation of a series of random letters or numbers and to respond to a target stimulus. Finally, shifting attention is the ability to flexibly shift ones attention from one focus or stimuli to another (Baron, 2004). Commonly administered tests of shifting attention include verbal and design fluency tests, which detect difficulties with the ability to shift in terms of perseverative errors (Baron, 2004).

Survivors of ALL treated with chemotherapy alone have been found to demonstrate impairments in a variety of subdomains of attention. In fact, attention is one of the domains most commonly found to be effected in studies of this population, with approximately one-fourth of survivors of ALL showing evidence of deficits in attention (Bisen-Hersh et al., 2011; Butler & Copeland, 2002). Specifically, studies have found evidence of impaired performance, relative to controls, on tests of selective (Ashford et al., 2010; Carey et al., 2008; Harila et al., 2009), divided (Carey et al., 2008; Kingma et al., 2002; Lesnik et al., 1998), sustained (Reddick et al., 2006), and shifting (Buizer et al., 2005) attention. These deficits may impact survivors' ability to maintain concentration and ignore distractions, which in turn may negatively impact their academic achievement and quality of life (Anderson & Kunin-Batson, 2009; Butler & Copeland, 2002).

Executive functioning.

Executive functioning (EF) is a somewhat nebulous concept within the field of neuropsychology, as several differing definitions and models of EF have been proposed but none have received universal acceptance (Baron, 2004). Various subcomponents of EF that have been proposed include planning, reasoning, cognitive flexibility, inhibition, initiation, and working memory (Anderson, 2002; Baron, 2004). Further complicating the conceptualization and assessment of EF is the fact that various aspects of EF overlap considerably with other domains of neurocognitive functioning such as attention and memory (Baron, 2004). However, the abilities that fall under the domain of EF are crucial to successful daily living and consideration of their intactness among survivors of pediatric ALL is critical (Anderson, 2002; Baron, 2004).

Researchers have proposed a developmental model of executive functioning based upon factor analysis and clinical neuropsychological knowledge (Figure 1; Anderson, 2002). In this model, EF is comprised of four distinct domains, referred to as: (a) attentional control, (b) information processing, (c) cognitive flexibility, and (d) goal setting. Although these domains are thought to be separate within this model, they are also thought to operate in an integrative manner in order to execute tasks. Thus, they can be conceptualized of as an overall control system (Anderson, 2002). Each of these domains subsumes a number of highly integrated cognitive processes.

Within this model of EF, the attentional control domain relates to the ability to selectively attend to certain stimuli, to inhibit certain responses, and to focus attention for a prolonged period of time (Anderson, 2002). Therefore, it consists of processes such as selective attention, self-regulation, self-monitoring, and inhibition. Deficits in attentional control are thought to be reflected by impulsive behavior, lack of self-control, failure to

complete tasks, the inability to self-correct procedural mistakes, and inappropriate responses to stimuli or situation.

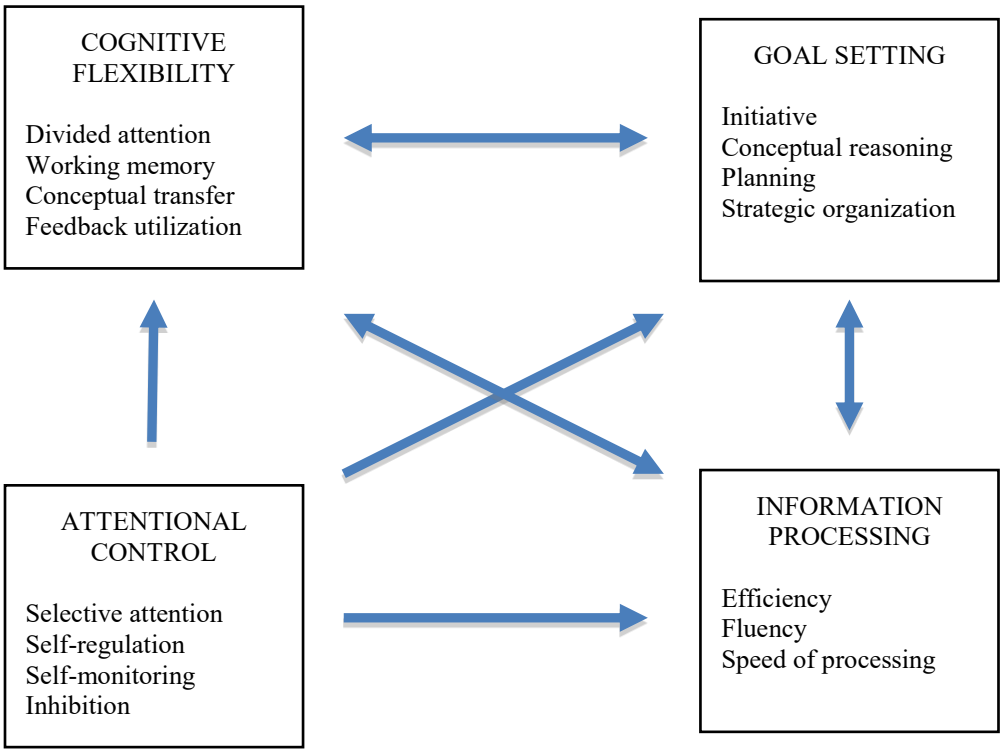

Figure 1: Anderson's developmental model of executive functioning.

The information processing domain refers to the ability to quickly and accurately process information (Anderson, 2002). It is thought to include processes such as efficiency, fluency, and processing speed. Deficits in this domain are reflected by reduced output, delayed responses, hesitancy, and slow reaction times.

The goal setting domain refers to the ability to develop new initiatives and concepts, to plan actions in advance, and to approach tasks in an efficient and strategic manner (Anderson, 2002). Aspects of this domain include initiative, conceptual reasoning, planning, and strategic organization. Deficits in this domain are thought to be

reflected by poor problem solving abilities, disorganization, poor planning, development of inefficient strategies, continued reliance on previously learned strategies even when they are no longer effective, and poor conceptual reasoning.

The cognitive flexibility domain refers to the ability to shift between cognitive sets, to learn from mistakes, to divide attention, to devise alternative strategies, and to simultaneously process multiple sources of information (Anderson, 2002). Components of this domain are divided attention, working memory, conceptual transfer, and feedback utilization. Deficits in this domain are reflected in rigidity and ritualistic behavior, difficulty with new activities or procedures, failure to adapt to new demands, and perseverative behavior such as continuing to make the same mistake or break the same rule regardless of feedback.

Studies have found that survivors of pediatric ALL treated with chemotherapy-only show evidence of deficits, relative to controls, in various aspects of executive functioning. These include cognitive flexibility/working memory (Ashford et al., 2010; Carey et al., 2008; Iver et al., 2015; Kingma et al., 2002; Lesnik et al., 1998; Waber et al., 1995), information processing/processing speed (Iver et al., 2015; Jansen, 2008), and attentional control/inhibition (Harila et al., 2009). These deficits have been found to underlie problems with behavior and school performance among survivors of ALL treated with chemotherapy-only protocols (Buizer et al., 2009). Furthermore, deficits in executive functioning have implications for survivors' long-term occupational and social functioning and their overall quality of life, as intact executive functioning is crucial to optimal academic, adaptive, and social functioning (Campbell et al., 2007; Winter et al., 2014).

Summary.

Overall, research shows that chemotherapy-only treatment for ALL, while perhaps less neurotoxic than CRT, is still associated with neurocognitive late effects (Iver et al., 2015; Riccio et al., 2010; Winick, 2011). Deficits in the areas of attention and executive functioning are particularly prevalent among this population (Anderson & Kunin-Batson, 2009; Campbell et al., 2007; Peterson et al., 2008; Riccio et al., 2010; Winick, 2011). These deficits may lead to real and significant impairments in the classroom setting (Nathan et al., 2007). Impairments in attention and executive functions such as working memory, cognitive flexibility, and inhibition have also been found to be associated with increased stress and problem behavior and decreased ability to use effective coping strategies among survivors of pediatric ALL, all of which impact the survivors' quality of life (Riccio et al., 2010). Survivors of pediatric ALL treated with chemotherapy alone who have neurocognitive deficits following their treatment have been found to be at risk for poor quality of life (Kunin-Batson, Kadan-Lottick, & Negila, 2014).

Risk and protective factors.

As understanding of the neurocognitive late effects of chemotherapy-only treatment for ALL improves, a prominent focus of research has become the risk and protective factors that serve to mediate and moderate the effects of the treatment. Traditionally the focus of this research has been on biologic moderators and mediators, including disease and treatment-related factors such as the intensity of the treatment regimen (Brouwers, 2005; Buizer et al., 2009). Children who have received intensified treatment, such as higher doses of systemic methotrexate, have been found to perform significantly worse than survivors treated on lower intensity protocols in a few studies (Buizer et al., 2005; Buizer et al., 2009). However, some studies examining differences in

outcome based on risk-group and treatment intensity have found that these differences are less pronounced than those related to child characteristics such as age at diagnosis and maternal education level (Waber et al., 2012). Such findings suggest that a focus on child-related and psychosocial risk factors is increasingly important for this population.

Child-related moderators of neurocognitive outcome include age at diagnosis, gender, time since diagnosis, and age at testing (Brouwers, 2008). Specifically, young age at diagnosis and female gender have been found to be risk factors for neurocognitive late effects following chemotherapy-only treatment for ALL (Buizer et al., 2009; Moleski, 2000; Peterson et al., 2008). Particularly, children younger than 5 years of age at the time of diagnosis have been found to be particularly vulnerable to cognitive dysfunction as a result of their treatment (Buizer et al., 2009). This is believed to be due to the fact that their brains, being less mature than those of older children, may be more vulnerable to the neurotoxicity of the treatments used for CNS prophylaxis (Buizer et al., 2009). In this case, age at treatment is seen as a proxy for the level of "neurodevelopmental maturity" of the child's brain (Mulhern & Palmer, 2003). Several studies have found that male survivors of pediatric ALL outperform female survivors on tests of neurocognitive functioning (Buizer et al., 2009). Effect-size statistics used in a meta-analysis on this literature confirmed the significance of the differential performances between male and female survivors (Peterson et al., 2008). Thus, girls appear to exhibit more late effects.

In addition to these child-related moderators, social and demographic moderators of neurocognitive outcome in this population have also been identified. Socioeconomic status (SES) has been identified as one such moderator in that differences in SES have been found to account for a significant amount of variability in neurocognitive outcome among this population (Stehbens et al., 1994; Winick, 2011). Specifically, survivors of

pediatric cancer from families with higher levels of SES have been found to have higher levels of neurocognitive functioning after treatment (Mulhern & Palmer, 2003). This is thought to be due to survivors from higher SES families being exposed to more enriched environments, which may help them overcome deficits more easily (Mulhern & Palmer, 2003).

Research has helped to clarify our understanding of the medical, treatment-related, child-related, and demographic factors that mediate and moderate neurocognitive outcome in survivors of pediatric ALL (Patel & Carlson-Green, 2005). However, much less is known about potential psychosocial moderators of neurocognitive outcome in this population (Anderson & Kunin-Batson, 2009). One specific potential psychosocial moderator of neurocognitive outcome that has not yet been explored among survivors of pediatric ALL is family functioning. Given evidence from the pediatric traumatic brain injury and pediatric brain tumor fields as to the effect that family variables have on neurocognitive outcome, it is worth exploring whether positive family functioning serves as a protective factor against neurocognitive late effects for survivors of pediatric ALL (Anderson & Kunin-Batson, 2009; Hocking et al., 2011; Nathan et al., 2007).

Family Functioning

From a family systems perspective, family functioning refers to a family's ability to engage in basic interactional patterns that enable them to achieve family goals (Walsh, 2011). There are several models of family functioning, but most include dimensions such as "family structure or organization, communication, cohesion, problem solving, and emotional expression" (Hocking et al., 2011, p. 945). One model of family functioning that is used quite often in research and clinical practice is the McMaster Model of Family

Functioning (MMFF), which was first described by Epstein, Bishop, and Levin in 1978 (Carlson, 2003; Epstein et al., 2003).

The McMaster Model of Family Functioning.

Grounded in systems theory, the MMFF views families as open systems that are comprised of various subsystems (i.e., parents, children) that relate to other, larger systems such as schools and extended family (Carlson, 2001; Epstein et al., 2003; Lebow & Stroud, 2011). Underlying the MMFF is the assumption that the primary purpose of the family unit is to facilitate the social, psychological, and biological growth and maintenance of its members (Epstein et al., 2003). According to this model, this purpose is achieved through the accomplishment of a variety of tasks, which the developers of the MMFF divide into three types: Basic Tasks, Developmental Tasks, and Hazardous Tasks (Epstein et al., 2003; Lebow & Stroud, 2011). Basic Tasks are the most fundamental and involve instrumental issues such as the provision of food, money, transportation, and shelter (Epstein et al., 2003). Developmental Tasks are the various stages that the family and its members face over time. These occur on both an individual level (i.e., infancy, childhood, adolescence, middle age, and old age) and a family level (i.e., the beginning of a marriage, a first pregnancy, or the "empty nest" after the last child leaves home; Epstein et al., 2003). Hazardous Tasks are crises that arise due to unexpected circumstances, such as accidents or job loss (Epstein et al., 2003). Inability for a family to effectively accomplish these three task areas has been found to be associated with the development of clinically significant problems and maladaptive family functioning (Epstein et al., 2003).

Dimensions of family functioning in the MMFF.

The MMFF identifies six dimensions of family functioning as being most important for the emotional and physical health of family members and the effective accomplishment of the tasks required of the family (Epstein et al., 2003; Lebow & Stroud, 2011). The six dimensions, which will be defined in greater detail, are: problem solving, communication, role functioning, affective responsiveness, affective involvement, and behavior control (Epstein et al., 2003; Lebow & Stroud, 2011). Within each dimension, the authors of the MMFF have identified practices and patterns of interaction that they deem to range from "most ineffective" to "most effective" (Epstein et al., 2003). "Most ineffective" functioning in a dimension is thought to lead to the development of clinically significant difficulties for the family, while "most effective" functioning in all dimensions is thought to contribute to "optimal physical and emotional health" among family members (Epstein et al., 2003, p. 582). Research on the MMFF has not found one dimension that serves to predict good or poor overall family functioning on its own; rather, all dimensions are thought to be important to understanding the overall function of a family (Epstein et al., 2003).

Problem solving.

Problem solving is defined within this model as the ability of a family to efficiently and easily resolve problems so as to maintain effective family functioning (Epstein et al., 2003; Lebow & Stroud, 2011; Miller, Ryan, Keitner, Bishop, & Epstein, 2000). The MMFF identifies two types of problems that families face: instrumental and affective (Epstein et al., 2003). Instrumental problems are those that relate to the provision of basic necessities of living, whereas affective problems are those relating to emotions and feelings (Epstein et al., 2003).

In the MMFF, effective problem solving can be broken down into seven sequential steps: (1) problem identification, (2) communication about the problem with appropriate people, (3) development of a set of possible solutions, (4) deciding which solution to pursue, (5) putting the solution into place, (6) monitoring the progress of solution implementation, and (7) evaluation of the effectiveness of the problem-solving process (Epstein et al., 2003). According to this theory, the process that a family engages in when faced with problems in need of solutions is more important than the content of those problems in determining the level of functioning of the family (Epstein et al., 2003). Highly functioning families tend to engage in these steps (discussing the issues, communicating with each other, deciding on and implementing an appropriate solution, etc.) whether the problem is relatively minor or is rather major, such as a job loss or terminal illness (Epstein et al., 2003).

The developers of the MMFF hypothesize that most effective functioning in this domain occurs when (a) both instrumental and affective problems are solved and (b) when all seven steps of the problem-solving process are preformed (Epstein et al., 2003). Least effective functioning is thought to occur when families are unable to complete even step one of the process, the identification of problems (Epstein et al., 2003).

Communication.

The second dimension of family functioning included in the MMFF is communication, which is defined within the model as the patterns of verbal information exchange that occur within the family (Epstein et al., 2003; Lebow & Stroud, 2011; Miller et al., 2000). The MMFF focuses on verbal, as opposed to nonverbal or behavioral, communication because it is more easily observed and measured (Epstein et al., 2003). Furthermore, it focuses on the overall family pattern of communication as opposed to

examining the individual communication styles of members of the family, as this has been found to be most helpful to families and family therapists in the clinical experience of the authors of the MMFF (Epstein et al., 2003).

As with problem solving, the MMFF divides communication into two areas, instrumental and affective (Epstein et al., 2003). In addition, the MMFF considers the style of communication in which the family engages. It does so along two independent continua, with one ranging from clear to masked and the other ranging from direct to indirect (Epstein et al., 2003). The clear vs. masked continuum refers to whether the message is expressed clearly or is vague and muddy. The direct vs. indirect distinction refers to whether the message is expressed to the intended recipient or to another member of the family (Miller et al., 2000).

Therefore, within the MMFF there are considered to be four possible styles of communication: clear and direct, clear and indirect, masked and direct, and masked and indirect (Epstein et al., 2003). To illustrate each of these four possible styles, imagine a situation in which a wife is angry with her husband for coming home late from work without calling. An example of clear and direct communication in this circumstance would be if she told him "I am upset that you are late and I wish you would have called to tell me you would be late." An example of clear and indirect communication would be if the wife told their daughter, in the presence of the husband, "I am upset with your father because he was late and did not call to tell me that he would be." An example of masked and direct communication would be if the wife said to her husband "Traffic must have been really bad for you to be getting home at this time." Finally, an example of masked and indirect communication would be if the wife told the daughter, in the presence of her husband, "It's really annoying when I don't know what time people are planning to be home for dinner." Although the model focuses on verbal communication, it does take into

account nonverbal behavior, especially in so far as it contradicts the information that is being verbally exchanged, as this is thought to reflect masking or indirectness or both (Epstein et al., 2003).

According to the MMFF, most effective functioning in this domain occurs when (a) the family is able to communicate well about both instrumental and affective matters and (b) when the communication is clear and direct (Epstein et al., 2003). Least effective functioning is thought to occur when the communication in the family is masked and indirect (Epstein et al., 2003).

Role functioning.

Within the MMFF, roles are defined as the patterns of behavior family members engage in so as to fulfill the family's functions (Epstein et al., 2003; Lebow & Stroud, 2011; Miller et al, 2000). According to the MMFF, there are five basic types of family functions that are necessary for the maintenance of an effective and healthy family system: provision of resources, nurturance and support, adult sexual gratification, personal development, and maintenance and management of the family system (Epstein et al., 2003). Each of these areas includes a number of tasks and functions. The 'provision of resources' area includes tasks and functions related to the attainment of food, clothing, shelter, and other basic human needs. The 'nurturance and support' area includes tasks related to providing members of the family with warmth, comfort, and reassurance. The 'adult sexual gratification' area involves ensuring that each adult partner is satisfied with the level of sexual intimacy present in the relationship. 'Personal development' tasks and functions include those related to the physical, emotional, educational, social, and professional development of each family member. Finally, the 'maintenance and management of the family system' area includes a variety of functions and tasks related

to decision making/leadership, boundaries, finances, discipline, and health (Epstein et al., 2003).

The MMFF identifies two aspects of role functioning that are deemed to be vital to effective family functioning: role allocation and role accountability (Epstein et al., 2003). Role allocation involves the family's patterns for the assignment of roles and role accountability refers to the ways in which the family ensures that roles are fulfilled (Epstein et al., 2003). An example is the task of taking out the trash, a part of the provision of resources area of family role functioning. The parents discussing amongst themselves who will be responsible for taking out the trash and deciding together that it will be their oldest son's job to do so would be an example of role allocation. The use of a sticker chart to monitor whether or not the son has accomplished this task would be an example of role accountability.

Most effective functioning occurs when all of the family functions have been clearly allocated to the appropriate family member(s) and when accountability is maintained (Epstein et al., 2003). Least effective functioning occurs when necessary family functions are unaddressed and when either allocation or accountability is not maintained (Epstein et al., 2003).

Affective responsiveness.

Affective responsiveness within the MMFF relates to the family's range of emotional responses to stimuli, both in terms of quality and quantity (Epstein et al., 2003; Lebow & Stroud, 2011; Miller et al., 2000). The qualitative aspect refers to the ability of the family to respond with a spectrum of human emotions, as well as whether or not the emotion experienced matches the stimuli and/or context (Epstein et al., 2003). The quantitative aspect refers to the degree of affective response expressed, and ranges from

absence of response to over-responsiveness, with reasonable or expected responsiveness in the middle (Epstein et al., 2003). The MMFF identifies two groups of affect: welfare emotions (such as love, joy, and concern) and emergency emotions (such as sadness, fear, and anger; Epstein et al., 2003).

Most effective functioning is defined as occurring when the family experiences a full range of qualitatively and quantitatively appropriate responses to stimuli. Least effective functioning occurs when only a narrow range of affect is experienced or when the amount and quality of affective responses are inappropriate for the context in which they occur (Epstein et al., 2003).

Affective involvement.

The MMFF defines affective involvement as the degree to which the family demonstrates interest in and values the activities and interests of individual family members (Epstein et al., 2003; Lebow & Stroud, 2011; Miller et al., 2000). This dimension focuses both on the amount of interest the family shows as well as the way(s) in which they demonstrate that interest (Epstein et al., 2003). The model identifies six types of affective involvement: lack of involvement, involvement devoid of feelings, narcissistic involvement, empathic involvement, overinvolvement, and symbiotic involvement (Epstein et al., 2003). These types exist on a continuum, with 'lack of involvement' at one extreme and 'symbiotic involvement' at the other.

'Lack of involvement' occurs when family members have no interest or investment in one another's lives. 'Involvement devoid of feelings' is when family members have a purely intellectual interest in one another. 'Narcissistic involvement' occurs when a family member is only interested in another family member to the extent that the other member's behavior reflects upon himself or herself. 'Empathic

involvement' takes place when family members' interest in each other is for the sake of the other person. 'Overinvolvement' happens when family members show an excessive amount of interest in one another. Finally, 'symbiotic involvement' occurs when family members are invested in one another to such an extreme and pathological extent that it is difficult to differentiate between the individual members of the family. Empathic involvement is thought to contribute to most effective functioning in this dimension, with symbiotic involvement and absence of involvement leading to least effective functioning (Epstein et al., 2003).

Behavior control.

The final dimension of family functioning within the MMFF, behavior control, is the pattern of standards and rules set by the family in order to handle the behavior of its members in a variety of situations (Epstein et al., 2003; Lebow & Stroud, 2011; Miller et al., 2000). These situations are grouped into three types: physically dangerous situations, situations involving psychobiological needs, and situations that involve interpersonal socialization, both within and outside of the family (Epstein et al., 2003). Each of these types of situations may require different sets of standards and rules from the family.

In addition to the standards and rules set by the family in these areas, the MMFF is also interested in the amount of latitude that the family allows relative to these standards and rules (Epstein et al., 2003). Included in the model are four styles of behavior control that vary in terms of standards and latitude: rigid behavior control, flexible behavior control, laissez-faire behavior control, and chaotic behavior control (Epstein et al., 2003). Rigid behavior control occurs when the family's standards for behavior are quite narrow and specific and the family allows for very little variation or negotiation between situations. In flexible behavior control, the standards set by the

family are reasonable and may vary or be negotiable depending on the context or situation. With laissez-faire behavior control, the family holds no standards for the behavior of its members, allowing members complete latitude regardless of the situation. Finally, a chaotic behavior control style consists of a random and unpredictable vacillation between the three previous styles of behavior control, such that members of the family never know what to expect. Most effective functioning is associated with a flexible behavior control style and least effective functioning is associated with a chaotic behavior control style (Epstein et al., 2003).

Family functioning in families of pediatric cancer survivors.

Consideration of family functioning is crucial to a comprehensive understanding of the experience of survivors of pediatric ALL because childhood cancer is in many ways a family affair (Alderfer et al., 2009; Butler & Copeland, 2006). Although most parents of children diagnosed with cancer are resilient and demonstrate good coping after a period of significant, but transient, distress, a substantial portion (approximately 25-30%) will experience increased or prolonged distress or psychopathology (Kearney, Salley, & Muriel, 2015). While rates of divorce do not appear to be any higher among parents of children with cancer than among the general population, parents of pediatric cancer patients are actually at greater risk for psychological difficulties than their children with cancer (Kazak et al., 2012; Syse, Loge, & Lyngstad, 2010). Siblings of pediatric cancer patients have been found to be at an increased risk for difficulties in emotional, social, and behavioral functioning (Gilleland et al., 2013). While severe psychopathology among siblings is rare and some siblings display no difficulties with psychosocial functioning, some siblings of pediatric cancer patients experience symptoms of anxiety and depression, poorer quality of life, and difficulties with academic and social

functioning (Gerhardt, Lehmann, Long, & Alderfer, 2015). Parents and siblings of pediatric cancer patients have also been found to demonstrate symptoms of post-traumatic stress (Alderfer et al., 2010; Kaplan, Kaal, Bradley, & Alderfer, 2013).

In addition to the challenges faced by each individual family member, a diagnosis of a potentially terminal illness such as ALL in a child poses a significant challenge to the functioning of that child's family as a whole (Alderfer et al., 2009). Many families demonstrate resiliency following pediatric cancer; however, a subset of families experience significant and long term difficulties with family functioning (Van Schoors, Caes, Verhofstadt, Goubert, & Alderfer, 2015). Families of children receiving cancer treatment have been found to demonstrate lower levels of functioning than families of children who have completed treatment, but even "off-treatment" families have been found to show evidence of long-term disruptions in family functioning (Alderfer et al., 2009). In addition, the presence of neurocognitive late effects among pediatric cancer survivors has been found to be associated with increased levels of stress among parents of the survivors and decreased levels of family functioning (Hocking, Hobbie, Deatrick, Hardie, & Barakat, 2015; Patel et al., 2013).

Research examining family functioning among adolescent survivors of childhood cancer and their families has found higher levels of self-reported difficulties in family functioning among this population (Alderfer et al., 2009). One study that used a self-report measure of family functioning based on the MMFF found that 35-62% of adolescent survivors and 17-44% of their parents reported poor levels of family functioning in at least one of the six dimensions of the MMFF (Alderfer et al., 2009). In that study, almost half of the adolescent survivors, one fourth of their mothers, and one third of their fathers reported poor family functioning on four or more of the dimensions of family functioning included in the MMFF (Alderfer et al., 2009). These levels of self-

reported difficulties with family functioning are much higher than are typically found among community samples, in which less than 10% report poor functioning on that many dimensions (Alderfer et al., 2009). This indicates that the six dimensions of family functioning included in the MMFF are very relevant areas to consider when working with survivors of childhood ALL and their families.

Family functioning and neurocognitive late effects in TBI.

Although the relationship between family functioning and neurocognitive functioning has not been studied among survivors of pediatric ALL, there is evidence from research on pediatric TBI that family variables, such as family functioning, may predict child neurocognitive outcomes following TBI (Hocking et al., 2011). Studies have found better family functioning to be positively associated with neurocognitive outcomes following pediatric TBI (Nadebaum et al., 2007). Researchers began investigating family influences on neurocognitive sequelae in pediatric TBI after it had been found that pediatric TBI has a negative impact on families (Taylor et al., 1999). It was thought that the negative impacts of TBI upon the family might in turn make it difficult for the family to adequately support the child's recovery from TBI (Taylor et al., 1999). Supporting this notion, there has been evidence linking family stress and ineffective parenting practices within the clinical literature (Taylor et al., 1999). Furthermore, studies performed on animals showed that environmental influences affected recovery of function (Taylor et al., 1999). Therefore, researchers in the field of pediatric TBI hypothesized that the long-term sequelae of pediatric TBI may be partially related to environmental factors such as family functioning (Taylor et al., 1999). As there have been no reviews or meta-analyses conducted on this literature to date, each study investigating the relationship between

family functioning and neurocognitive outcome following pediatric TBI will be examined individually.

Yeates and colleagues (1997) examined the influence of injury severity and preinjury social environment on neurocognitive outcomes among children with severe TBI, moderate TBI, and a comparison group of children with orthopedic injuries (OI). They assessed premorbid child and family characteristics during a baseline assessment shortly after the children's injuries and child neurocognitive functioning was assessed at baseline and approximately 6 and 12 months postinjury (Yeates et al., 1997). They used growth curve analysis to test three hypotheses regarding the influence of injury severity and pre-injury social environment on neurocognitive outcome (Yeates et al., 1997). The measures of pre-injury family environment, which were used a predictors of neurocognitive outcomes, included the Family Assessment Device (FAD), a measure of family functioning based upon the MMFF (Yeates et al., 1997). There were three measures of cognitive functioning chosen as dependent variables. The first was a prorated Performance Scale IQ (PIQ) derived from a short form of the Wechsler Intelligence Scale for Children – Third Edition (WISC-III), which was used as a measure of nonverbal skills that has been found to be sensitive to the acute effects of TBI in children. The second measure of cognitive functioning was the total raw score from the Developmental Test of Visual–Motor Integration (VMI), a drawing task that requires visuoperceptual, constructional, and graphomotor skills and has been shown to be sensitive to TBI in children. The final measure of cognitive functioning used was the total number of words recalled across five learning trials on a shortened, preliminary version of the children's California Verbal Learning Test (CVLT), a word-list learning task that measures verbal memory skills. Total recall on the CVLT has been shown to discriminate between children with TBI and matched controls.

Yeates and colleagues (1997) found that the four family variables included in their analysis accounted for significant amounts of variance in each of their outcome measures, even after controlling for injury severity (group membership). In fact, the preinjury family environment accounted for a larger amount of variance in outcome at 12 months post-injury than did injury severity. After controlling for injury severity and demographics, family environment accounted for as much as 25% of the variance in cognitive outcome following TBI.

Furthermore, they found that family functioning moderated the effect of TBI in that children from families with above-average family functioning tended to experience a more rapid and complete recovery from TBI, while children from families with below-average family functioning tended to experience a slower and less complete recovery. Specifically, below average family functioning was associated with lower amounts of cognitive improvement over the course of the first year postinjury and worse cognitive outcomes at 12-months post injury. For example, the difference between the severe TBI and the OI groups in total recall scores on the CVLT at 12-months postinjury was directly proportional to measured family functioning. For children whose FAD scores reflected above-average family functioning (i.e., scores were 1 standard deviation below the mean, as lower scores on the FAD reflect better family functioning), the group difference was only 2.69 words. However, for children whose FAD scores were reflective of below-average family functioning (i.e., 1 standard deviation above the mean), the difference between the severe TBI and the OI groups was 9.23 words. Therefore, a difference of 2 standard deviations on the FAD resulted in a more "than 1 standard deviation increase in the discrepancy between the OI and severe TBI groups" in memory functioning (Yeates et al., 1997, p. 626).

The results of this study support the notion that family variables help to determine children's neurocognitive functioning following TBI and that the child's family environment moderates the impact of TBI (Yeates et al., 1997). Specifically, this study found that the deficits in memory functioning that are associated with severe TBI were cushioned by above-average family functioning and made worse by below-average family functioning (Yeates et al., 1997). Furthermore, their finding that environmental measures such as family functioning accounted for at least as much, or more, variance in level of neurocognitive outcome than did measures of injury severity suggests that the child's eventual neurocognitive functioning following a TBI depends as much, if not more, on environmental influences than on injury-related variables (Yeates et al., 1997).

In a later report on findings extending this research by Yeates and colleagues, Taylor et al. (1999) examined whether postinjury family environment was related to concurrent child outcomes in TBI. They looked at three aspects of the family environment: family dysfunction, parental psychological distress, and injury-related family burden (Taylor et al., 1999). They assessed patients at baseline (shortly after injury), at 6 months postbaseline, and at 12 months postbaseline (Taylor et al., 1999). There were three groups of children included in the study: children with severe TBI, children with moderate TBI, and children with an orthopedic injury not involving insult to the CNS (Taylor et al., 1999). The orthopedic group was included in order to control for possible confounding variables such as proneness to accidents, the experience of hospitalization, and practice effects from repeated testing, as well as to examine possible differential consequences of TBI as opposed to non-CNS related injury (Taylor et al., 1999). As with the previous report, the measure of family functioning used in this study was the General Functioning scale of the FAD (Taylor et al., 1999). However, a much more comprehensive neurocognitive test battery was administered to the patients in this

aspect of the study. The specific domains examined included global cognitive ability, language skills, perceptual-motor skills, memory, attention, academic achievement, school performance, behavior problems, child competence, and adaptive behavior.

They examined the influence of post-injury family status at the 6- and 12-month follow-ups on concurrent child outcomes via hierarchical linear regression (Taylor et al., 1999). This study found that these post-injury measures of family function were associated with concurrent child outcomes at both the 6- and 12-month follow-ups (Taylor et al., 1999). Higher levels of concurrent family functioning were associated with better child functioning, even after controlling for injury severity and pre-injury family functioning (Taylor et al., 1999). Furthermore, they found an interaction between group contrasts and family functioning, such that the group effect of severe TBI vs. orthopedic group interacted with the FAD-GF in predicting verbal memory, math skills, and teacher ratings of academic performance (Taylor et al., 1999). Specifically, this study found that the differences in outcomes between severe TBI and orthopedic injury in these domains were more pronounced in children from families with higher levels of dysfunction at both 6- and 12-months post baseline (Taylor et al., 1999).

Other studies have also found support for a link between family functioning and memory functioning among pediatric TBI patients. Max and colleagues used the McMaster Structured Interview of Family Functioning (Mc-SIFF), a clinical research interview based upon the MMFF, to assess family functioning (Max et al., 1999). The Mc-SIFF is used in order to obtain scores on a rating scale named the Clinical Rating Scale (CRS), which contains seven items corresponding to the seven domains of family functioning included in the MMFF (Max et al., 1999). They utilized the global score from the CRS in their analyses (Max et al., 1999). Max and colleagues (1999) assessed intellectual and memory functioning among children with severe traumatic brain injuries,

mild traumatic brain injuries, and orthopedic injuries using the WISC-R and the WRAML. Specifically, they used a prorated PIQ score, a prorated VIQ score, and a FIQ score from a short form of the WISC-R and a Verbal Memory Index and Visual Memory Index from the WRAML in their analyses. Max and colleagues began with eight independent variables: family psychiatric history, duration of impaired consciousness, family functioning, lowest post-resuscitation score on the Glasgow Coma Scale (a measure of responsiveness to stimuli following a TBI), neurological exam, "novel" post-injury psychiatric disorder, pre-injury psychiatric disorder, and socioeconomic status (Max et al., 1999).

The researchers found that intellectual and memory function outcome in pediatric brain injury was significantly related to a Psychosocial Disadvantage Factor that included family dysfunction (Max et al., 1999). Notably, this study found that family functioning, together with family psychiatric history, added significantly to SES in explaining cognitive outcomes two years after injury. While causation certainly could not be inferred from this cross-sectional study, the results do suggest that psychosocial disadvantage factors such as poor family functioning influence children's cognitive outcomes from TBI (Max et al., 1999). This study supported the findings of Yeates et al. and Taylor et al., and added findings related to family functioning having an effect on general intellectual functioning after pediatric brain injury as well.

A more recent study found similar results in the domains of attention/executive functioning. Nadebaum and colleagues investigated long-term attention/executive functioning among survivors of pediatric TBI (Nadebaum et al., 2007). Their study consisted of 54 children who had sustained a TBI and 17 healthy control subjects who were selected to match the TBI group as closely as possible in terms of age, gender, SES, and pre-injury abilities (Nadebaum et al., 2007). Family functioning was assessed using

the Family Functioning Questionnaire (FFQ), which parents completed at baseline and five years post-injury (Nadebaum et al., 2007). They used four cognitive measures to assess the various subcomponents of EF included in Anderson's model (Anderson, 2002). These included Sky Search from the Test of Everyday Attention for Children (TEA-Ch) for attentional control (sustained attention), Score DT from the TEA-Ch for cognitive flexibility (divided attention), Block Design from the Wechsler Intelligence Scales for Children-III (WISC-III) for goal setting (organization and perceptual reasoning), and the Processing Speed Index from the WISC-III (a composite of the Coding and Symbol Search subtests) for information processing (efficiency and speed of information processing). They also administered the Parent Form of the Behavior Rating Inventory of Executive Function (BRIEF), a rating scale that measures behavioral manifestations of executive dysfunction. The BRIEF was administered at baseline and five years post-injury, whereas the cognitive measures were only administered five years post-injury.

As with Taylor et al. (1999), Nadebaum and colleagues (2007) utilized hierarchical linear multiple regression analyses to identify factors that predicted EF outcome. They found that pre-injury family functioning was a significant predictor of Processing Speed Index scores, with higher scores associated with higher levels of family functioning. Family functioning also significantly predicted overall EF outcome (performance on the composite measure of EF), with better pre-injury family functioning again associated with better outcomes.

Summary.

Using different measures of family functioning, researchers have identified a protective influence on children's immediate and longer-term recovery from traumatic brain injury. Pre-injury family functioning, as reported at the time of injury, explained

significant amounts of variance in executive functioning, memory, and intellectual outcomes at 6- and 12-months as well as 2- and 5-years postinjury (Max et al., 1999; Nadebaum et al., 2007; Yeates et al., 1997). Concurrent family functioning was also found to explain significant amounts of variance in memory and academic achievement at 6- and 12-months postinjury (Taylor et al., 1999). One interpretation of the findings of these studies is that the neurocognitive effects of TBI make these children more vulnerable to family influences than their peers who have not sustained a head injury (Taylor et al., 1999). Also, it could be that families with higher levels of dysfunction lack the ability to adequately support the child's recovery from TBI, such that the child does not have enough opportunity or motivation necessary to perform the practice of cognitive skills that is necessary for a more complete neurocognitive recovery from TBI (Taylor et al., 1999). Another interpretation is that a positive family environment actually facilitates neural recovery (Taylor et al., 1999). This hypothesis has been supported in studies with animals, but has little empirical support to date from studies of human recovery of function (Taylor et al., 1999).

Family functioning and neurocognitive late effects in pediatric brain tumors.

In one of the only studies to examine the impact of family functioning on neurocognitive functioning among pediatric cancer patients, Carlson-Green and colleagues investigated the ability of family measures to predict the cognitive functioning of 63 children being treated for brain tumors (Carlson-Green et al., 1995). They used hierarchical multiple regression to determine whether or not family variables improved prediction of child outcomes over and above illness variables and covariates. Illness variables included measures of neurological symptoms and treatment severity. Family predictors included the total scale score from the Coping Health Inventory for Parents

(CHIP) as a measure of maternal coping resources, the total family stress score from the Family Inventory of Life Events (FILE) as a measure of family stressors, and the Cohesion and Control scales from the Family Environment Scale (FES) as measures of the family environment. Cognitive outcome variables included the Composite Standard Score from the Stanford-Binet Intelligence Scale: Fourth Edition as a measure of intelligence and the average standard score across reading, spelling, and arithmetic on the Wide Range Achievement Test – Revised (WRAT-R) as a measure of achievement. The covariates included in the model were time since diagnosis, SES, age at diagnosis, and parental marital status. In terms of cognitive outcomes, they found that family variables did explain a significant amount of variance in child intellectual outcome, with the most parsimonious model including both family (maternal coping resources) and illness (treatment severity) measures, as well as covariate measures (time since diagnosis, SES, and marital status). Family variables did not account for any additional variance above illness factors in predicting child achievement outcomes.

Ach and colleagues examined the relationship between family functioning and academic achievement among pediatric brain tumor survivors (Ach et al., 2012). They administered the Wide Range Achievement Test – Third Edition (WRAT-3), a demographic data form, and the FES to pediatric brain tumor survivors between the ages of 8 and 15 who were 1 to 5 years posttreatment as well as classmate controls who were matched for age, gender, and race. They found that survivors from families with lower levels of support and higher levels of conflict demonstrated deficits in achievement relative to the classmate-controls across the domains of reading, spelling, and arithmetic, even after controlling for age at diagnosis, time since treatment, and type of treatment. The authors speculated that families with higher levels of support and lower levels of

conflict may devote more time and attention to helping survivors develop academic skills, allowing them to overcome neurocognitive late effects from treatment.

A recent study examined the relationship between family functioning and neurocognitive functioning among young-adult aged survivors of pediatric brain tumor, as well as the role of family functioning in mediating the association between neurocognitive functioning and health-related quality of life (HRQOL) among this population (Hocking et al., 2015). Neurocognitive functioning was assessed using the Wechsler Adult Intelligence Scaled – Fourth Edition (WAIS-IV) Working Memory Index as a measure of auditory working memory, the WAIS-IV Processing Speed Index as a measure of processing speed, the California Verbal Learning Test – Second Edition Short Form (CVLT-II SF) long delay recall z-score as a measure of auditory verbal memory, and the Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test switching task scaled score and Tower Test scaled achievement score as measures of executive functioning. They assessed survivor- and mother-reported family functioning using the Family Assessment Device General Functioning Scale (FAD GFS) and mother-reported family functioning using the PedsQL Family Impact Module (PedsQL FIM) Family Functioning scale score. Mothers of survivors completed the Pediatric Oncology Quality of Life Scale (POQOLS) as a proxy-report measure of survivor HRQOL.

Correlational analyses indicated that worse processing speed, working memory, verbal memory, and executive functioning were significantly associated with worse survivor- and mother-reported family functioning. Further, bootstrapping analyses indicated that neurocognitive variables had an indirect effect on survivor HRQOL through mother-reported family functioning as measured by the PedsQL FIM. However, mother-reported family functioning on the FAD GFS did not support the indirect effects of the neurocognitive variables on survivor HRQOL. Survivor-reported FAD GFS scores

were not included in bootstrapping analyses, as they were not found to be related to HRQOL in correlational analyses. Results of this study indicate that survivors of pediatric brain tumor with greater neurocognitive late effects report greater difficulties with family functioning, as do the mothers of these survivors. This study provides support for the connection between family functioning and neurocognitive functioning among survivors of pediatric cancer and supports the rationale for the importance of the family context when considering neurocognitive late effects of pediatric cancer treatment.

Summary.

In summary, research from the fields of pediatric traumatic brain injury and pediatric brain tumors has shown that psychosocial variables such as family functioning moderate neurocognitive outcomes among these populations (Ach et al., 2013; Carlson-Green et al., 1995; Max et al., 1999; Nadebaum et al., 2007; Taylor et al., 1999; Yeates et al., 1997). Specifically, positive family functioning has been found to serve as a protective factor against the development of neurocognitive deficits in areas of neurocognitive functioning typically affected by TBI and brain tumors. This phenomenon has not yet been studied among survivors of pediatric ALL.

Statement of the Problem

Some variables that seem to moderate neurocognitive outcome among survivors of pediatric ALL treated with chemotherapy-only have been identified, including gender, age at diagnosis, time since diagnosis, and socioeconomic status (Brouwers, 2005; Buizer et al., 2009; Moleski, 2000; Mulhern & Palmer, 2003; Patel & Carlson-Green, 2005; Peterson et al., 2008; Stehbens et al., 1994; Waber et al., 2012; Winick, 2011). However, much less is known about potential psychosocial moderators such as family functioning (Anderson & Kunin-Batson, 2009; Patel & Carlson-Green, 2005). Evidence from the

pediatric traumatic brain injury and pediatric brain tumor populations suggests that positive family functioning serves as a protective factor for neurocognitive outcomes of children who survive these conditions (Ach et al., 2013; Carlson-Green et al., 1995; Max et al., 1999; Nadebaum et al., 2007; Taylor et al., 1999; Yeates et al., 1997). No known research has been completed to investigate whether positive family functioning similarly moderates the effects of CNS-directed chemotherapy on the neurocognitive functioning of survivors of pediatric ALL. Identification of all possible protective factors for neurocognitive outcomes among survivors of pediatric ALL is necessary in order to design, research, and implement effective interventions in an effort to decrease the prevalence of neurocognitive late effects among this population.

Statement of Purpose

The purpose of this study was to examine the effect of family functioning upon neurocognitive outcome among survivors of pediatric ALL treated with chemotherapy. Specifically, the study sought to determine if positive family functioning serves as a protective factor against the neurocognitive deficits commonly seen in this population. Based upon a multidimensional model of attention and Anderson's model of executive function (EF), four subcomponents of attention and four subcomponents of EF were examined (Anderson, 2002). The attention subcomponents were: selective, divided, sustained, and shifting. The EF subcomponents were: cognitive flexibility (working memory), goal setting (planning), attentional control (inhibition), and information processing (processing speed). In addition, caregiver report of the child's attention and EF was examined as well. It was hypothesized that family functioning would add to such moderating factors as age at diagnosis, gender, time since diagnosis, and SES in predicting neurocognitive outcome in the domains listed above.

Research Questions, Hypotheses, and Rationale

Research question 1.

Does positive family functioning protect against deficits in attention among survivors of pediatric ALL, specifically in the subdomains of selective attention, divided attention, sustained attention, and shifting attention, and as reported by caregivers?

Hypothesis 1a.

Family functioning is expected to moderate the impact of group membership (survivor vs. healthy control) on performance on a task of selective attention. Furthermore, differences in family functioning will account for a significant amount of the variance in performance on a task of selective attention for survivors of pediatric ALL but not for healthy controls.

Hypothesis 1b.

Family functioning is expected to moderate the impact of group membership (survivor vs. healthy control) on performance on a task of divided attention. Furthermore, differences in family functioning will account for a significant amount of the variance in performance on a task of divided attention for survivors of pediatric ALL but not for healthy controls.

Hypothesis 1c.

Family functioning is expected to moderate the impact of group membership (survivor vs. healthy control) on performance on a task of sustained attention. Furthermore, differences in family functioning will account for a significant amount of the variance in performance on a task of sustained attention for survivors of pediatric ALL but not for healthy controls.

Hypothesis 1d.

Family functioning is expected to moderate the impact of group membership (survivor vs. healthy control) on performance on a task of shifting attention. Furthermore, differences in family functioning will account for a significant amount of the variance in performance on a task of shifting attention for survivors of pediatric ALL but not for healthy controls.

Hypothesis 1e.

Family functioning is expected to moderate the impact of group membership (survivor vs. healthy control) on scores on caregiver ratings of attention. Furthermore, differences in family functioning will account for a significant amount of the variance in scores on caregiver ratings of inattention for survivors of pediatric ALL but not for healthy controls.

Rationale.

Survivors of pediatric ALL treated with chemotherapy have been found to have deficits in selective, divided, sustained, and shifting attention and in caregiver ratings of attention (Anderson & Kunin-Batson, 2009; Ashford et al., 2010; Bisen-Hersh et al., 2011; Butler & Copeland, 2002; Carey et al., 2008; Harila et al., 2009; Kingma et al., 2002; Lesnik et al, 1998; Reddick et al., 2006). Family functioning has been found to moderate neurocognitive outcome in survivors of pediatric traumatic brain injury and brain tumor in domains sensitive to insult in those populations (Carlson-Green et al., 1995; Max et al., 1999; Nadebaum et al., 2007; Taylor et al., 1999; Yeates et al., 1997). It is expected that family functioning will similarly moderate neurocognitive outcomes in the ALL population in attention, a domain sensitive to insult in this population. Furthermore, it is expected that positive family functioning will serve as a protective

factor against the development of attention problems among survivors of pediatric ALL. It is thought that higher functioning families may be better able to manage survivors' neurocognitive late effects, for example, by providing opportunities for the survivor to practice and strengthen the attentional skills that have been negatively impacted by the chemotherapy treatment. In alignment with Rose and colleagues' conceptualization of protective factors as operating only in instances of adversity, it is expected that children in the healthy control group, who have not been exposed to adversity in the form of CNS prophylaxis, will not demonstrate the same relationship between family functioning and performance on measures of attention (Rose, Holmbeck, Coakley, & Franks, 2004).

Research question 2.

Does positive family functioning protect against deficits in executive functioning among survivors of pediatric ALL, specifically in the subdomains (areas) of cognitive flexibility (working memory), goal setting (planning), attentional control (inhibition), information processing (processing speed) and as reported by caregivers?

Hypothesis 2a.

Family functioning is expected to moderate the impact of group membership (survivor vs. healthy control) on performance on a task of cognitive flexibility (working memory). Furthermore, differences in family functioning will account for a significant amount of the variance in performance on a task of cognitive flexibility (working memory) for survivors of pediatric ALL but not for healthy controls.

Hypothesis 2b.

Family functioning is expected to moderate the impact of group membership (survivor vs. healthy control) on performance on a task of goal setting (planning). Furthermore, differences in family functioning will account for a significant amount of

the variance in performance on a task of goal setting (planning) for survivors of pediatric ALL but not for healthy controls.

Hypothesis 2c.

Family functioning is expected to moderate the impact of group membership (survivor vs. healthy control) on performance on a task of attentional control (inhibition). Furthermore, differences in family functioning will account for a significant amount of the variance in performance on a task of attentional control (inhibition) for survivors of pediatric ALL but not for healthy controls.

Hypothesis 2d.

Family functioning is expected to moderate the impact of group membership (survivor vs. healthy control) on performance on a task of information processing (processing speed). Furthermore, differences in family functioning will account for a significant amount of the variance in performance on a task of information processing (processing speed) for survivors of pediatric ALL but not for healthy controls.

Hypothesis 2e.

Family functioning is expected to moderate the impact of group membership (survivor vs. healthy control) on scores on caregiver ratings of an aspect of executive functioning (behavioral regulation). Furthermore, differences in family functioning will account for a significant amount of the variance in scores on caregiver ratings of behavioral regulation for survivors of pediatric ALL but not for healthy controls.

Hypothesis 2f.

Family functioning is expected to moderate the impact of group membership (survivor vs. healthy control) on scores on caregiver ratings of another aspect of

executive functioning (metacognition). Furthermore, differences in family functioning will account for a significant amount of variance in scores on caregiver ratings of metacognition for survivors of pediatric ALL but not for healthy controls.

Rationale.

Survivors of pediatric ALL treated with chemotherapy have been found to have deficits in executive functioning, including working memory, inhibition, processing speed, and planning, and on caregiver ratings of executive functioning (Ashford et al., 2010; Buizer et al., 2009; Harila et al., 2009; Jansen et al., 2008; Kingma et al., 2002; Lesnik et al., 1998; Waber et al., 1995). Family functioning has been found to moderate neurocognitive outcome in survivors of pediatric traumatic brain injury in the domain of executive functioning (Nadebaum et al., 2007). It is expected that a similar moderating effect of family functioning on executive functioning will exist among the ALL population. Moreover, it is expected that positive family functioning will serve as a protective factor against the development of deficits in executive functioning among survivors of pediatric ALL. As such, it is expected that children in the healthy control group, who have not been exposed to adversity in the form of CNS prophylaxis, will not demonstrate the same relationship between family functioning and performance on measures of attention (Rose et al., 2004).

Chapter 3: Method

Participants

Participants were 20 children and adolescents who had completed chemotherapy-only treatment for ALL and 20 healthy control participants, as well as one parent or guardian for each youth participant, equaling a total of 40 dyads of children and their caregivers (N = 40 caregiver/child dyads). All youth participants were within the ages of 8 and 16.

For the experimental group in this study, the following inclusion criteria applied: (i) aged 8 years 0 months through 15 years 11 months throughout the length of the study, (ii) two years post-treatment and designated as a survivor of pediatric ALL by the Survivorship Center at the Children's Blood and Cancer Center (CBCC) at Dell Children's Medical Center (DCMC), and (iii) English-speaking. English language was required because most of the standardized measures used in this study were only in English and were not validated in other languages. Individuals meeting school criteria as having a visual or auditory impairment or attention difficulties such as attention-deficit/hyperactivity disorder (ADHD) prior to their cancer diagnosis were excluded from the study. Additionally, individuals who underwent a bone marrow transplant or cranial radiation therapy, had a recurrence of cancer, or who had impaired global cognitive functioning (e.g. intellectual disability) were not included in this investigation.

For the control group, the following inclusion criteria applied: (iii) aged 8 years 0 months through 15 years 11 months throughout the length of the study and (iv) English-speaking. Individuals meeting school criteria as having a visual or auditory impairment or attention difficulties such as attention-deficit/hyperactivity disorder (ADHD) and those with impaired global cognitive functioning (e.g., intellectual disability) were not included in this study.

The mean age for the overall sample was 11.36 (SD = 2.32, Range = 8.01-15.83). The mean age for the experimental group was 12.11 (SD = 2.47, Range = 8.36-15.83), while the mean age for the control group was 10.62 (SD = 1.93, Range = 8.01-13.72). There was a significant difference in the mean ages of the two groups, such that mean age for the experimental group was significantly higher than the mean age for the control group (t [38, 2]= -2.128, p = .04). In the experimental group, the mean age at diagnosis was 4.22 (SD = 2.44, Range = 1.32-10.01) and the mean time since treatment was 5.27 years (SD = 2.09, Range = 2.62-10.32). Additional demographic characteristics for the sample appear in the next chapter.

Instrumentation

Youth participants were administered measures of attention and executive functioning, and parent/guardians completed questionnaires about their child's attention and executive functioning and their family's functioning.

Attention measures.

Test of Everyday Attention – Children's Version (TEA-Ch). The Test of Everyday Attention for Children (TEA-Ch; Manly, Robertson, Anderson, & Nimmo-Smith, 1999) is a children's adaptation of the adult Test of Everyday Attention (TEA). It has been used in research with males with Fragile X syndrome, girls with Turner's syndrome, and children with head injury, ADHD, and learning disabilities (Baron, 2004). The full TEA-Ch is comprised of 9 subtests and a full administration takes approximately 1 hour. However, there is also a four-subtest screener version that takes 20-25 minutes to administer and assesses each of the four dimensions of attention (selective, divided, sustained, and shifting). The normative sample for the TEA-Ch included 293 Australian children and adolescents between the ages of 6 years, 7 months and 15 years, 11 months

and included equal numbers of males and females. The sample was divided into six age bands, with 29 to 58 children in each age band. Reported test-retest reliabilities for the TEA-Ch range from .57 to .87, with percentage agreement values ranging from 71% to 76% (Manly et al, 1999). A structural equation modeling study involving the normative sample resulted in a three-factor model of sustained attention, attentional control/switching, and selective attention (Manly et al., 2001).

The four-subtest screener version of the TEA-Ch was used in this study to assess the four subdomains of attention described previously. The specific subtests that were administered are: Sky Search, Score!, Creature Counting, and Sky Search DT. Sky Search is a measure of selective attention that requires the subject to filter information in order to detect relevant information while rejecting or inhibiting distracting information (Baron, 2004; Manly et al., 1999). The reported test-retest correlation coefficient from the normative sample for this subtest was 0.75. In the normative sample, scores on Sky Search demonstrated low levels of correlation with scores on subtests of an IQ test ($p > .01$, $p < .001$ required for statistical significance when full correction for multiple comparison was used), suggesting discriminant validity (Manly et al., 2001). Sky Search correlated with a different measure of selective attention (Stroop task, $p < .001$). There are three scores available for this subtest: an accuracy score, a timing score, and an overall attention score. For the purposes of this study, the attention score was used to measure selective attention.

Score! is a measure of sustained attention that requires the subject to count tones played on an audio recording and report the correct number of tones at the end of each round (Baron, 2004; Manly et al., 1999). The reported percentage agreement from the normative sample for this subtest was 76.2%. Scores on this measure from the normative sample demonstrated low levels of correlation with scores on subtests of an IQ test ($p >$

.05; Manly et al., 2001). Creature Counting is a measure of shifting attention that requires the subject to count stimuli according to visual cues indicating for them to count either upwards or downwards (Baron, 2004; Manly et al., 1999). There are two scores available for this subtest: an accuracy score and a timing score. The accuracy score was used as a measure of shifting attention. The reported test-retest correlation coefficient from the normative sample for this measure was 0.71. When corrections for multiple correlations were performed, Creature Counting accuracy scores from the normative sample were not significantly correlated with scores on IQ measures ($p > .001$; Manly et al., 2001). Sky Search DT is a measure of divided attention that requires the subject to circle certain stimuli while also keeping count of auditory tones (Baron, 2004; Manly et al., 1999). The reported test-retest correlation coefficient from the normative sample for this subtest was 0.81. Scores on Sky Search DT within the normative sample were not significantly correlated with scores on IQ measures ($p > .01$; Manly et al., 2001).

Behavior Assessment System for Children – Second Edition (BASC-2). The Behavior Assessment System for Children – Second Edition (BASC-2; Reynolds & Kamphaus, 2004) is a comprehensive set of rating scales and forms that assess behavioral and emotional functioning of children and adolescents and includes teacher, parent, and self-report versions. There are various forms of each of the three versions for use with different age groups, ranging from 2 years old through college age. For this study, the child (ages 6 to 11) and adolescent (ages 12 to 21) forms of the Parent Rating Scales (PRS) were used. These scales contain a number of items (134-160) that describe specific patterns of behavior and are rated on a four-point frequency scale ranging from “never” to “almost always.” The child and adolescent forms of the BASC-2 PRS were each standardized on a sample of 1,800 individuals representative of the U.S. population in terms of socioeconomic status, race/ethnicity, and geographic region according to figures

from the March 2001 Current Population Survey. For the purposes of this study, the "Attention Problems" subscale from the PRS was used in assessing parental report of children's attentional abilities. Reported coefficient alpha reliabilities from the normative sample for the attention problems scale on the child and adolescent forms of the PRS range from .85 to .88. Adjusted test-retest reliability coefficients for this scale are 0.81 for the adolescent form and 0.85 for the child form.

Executive functioning measures.

Delis-Kaplan Executive Function System (D-KEFS). The Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) is a standardized battery of tests that measure a variety of executive functions in people age 8 through 89 years. The D-KEFS was standardized on a nationally representative sample of 1750 people ages 8-89 years. The sample was stratified in regards to age, sex, race/ethnicity, years of education, and geographic region using figures from the 2000 U.S. Census. For this study, the following two subtests of the D-KEFS were administered: the D-KEFS Tower Test and the D-KEFS Color-Word Interference Test. The D-KEFS Tower Test is a measure of planning (Baron, 2004; Delis et al., 2001). A number of scores are available for the Tower Test; for this study, the Total Achievement scaled score was used as a measure of planning. Reported internal consistency values for this measure for children ages 8-16 ranged from 0.43 to 0.84. The reported test-retest reliability coefficient for this age group was 0.51. The D-KEFS Color-Word Interference Test is a measure of inhibition (Baron, 2004; Delis et al., 2001). Again, a number of scores are available for the Color-Word Interference Test. The Trial 3: Inhibition time scaled score was used as a measure of inhibition. The reported test-retest reliability coefficient for this measure for children ages 8-16 was 0.90.

Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV). The Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV; Wechsler, 2003) is a widely used measure of cognitive ability. It is comprised of fifteen subtests, ten in the core battery and five that are supplemental. It is designed for children age 6:0 through 16:11 and takes 65 to 80 minutes to administer in full. The WISC-IV yields a measure of global cognitive ability, the Full Scale IQ (FSIQ), as well as four composite scores: the Verbal Comprehension Index (VCI), the Perceptual Reasoning Index (PRI), the Working Memory Index (WMI), and the Processing Speed Index (PSI). The WISC-IV was standardized on a nationally representative sample of 2,200 children, stratified according to March 2000 U.S. Census data along the variables of age, sex, race/ethnicity, parent education level, and geographic region.

For the purposes of this study, four subtests of the WISC-IV were administered to participants. These are the Digit Span and Letter-Number Sequencing subtests, which together comprise the WMI, and the Symbol Search and Coding subtests, which together comprise the PSI. The WMI was used as a measure of working memory and the PSI was used as a measure of processing speed. Digit Span consists of two parts, Digit Span Forward (DSF) and Digit Span Backward (DSB). On DSF, the subject is required to repeat verbatim numbers presented to them orally. On DSB, the subject has to repeat numbers in the reverse order of that in which they are presented. Scores on these two components are combined to produce a total Digit Span scaled score. The reported overall average reliability coefficient from the normative sample for this subtest was 0.87. Letter-Number Sequencing requires the subject to listen to strings of mixed numbers and letters and to repeat the string with numbers first, in numerical order, followed by letters in alphabetical order. The reported overall average reliability coefficient from the normative sample for this subtest was 0.90. Symbol Search requires

the subject to visually scan a group of stimuli and indicate whether or not a target stimulus is present. The reported overall average reliability coefficient from the normative sample for this subtest was 0.79. Coding requires the subject to copy symbols paired with shapes or numbers within a given time limit. The reported overall average reliability coefficient from the normative sample for this subtest was 0.85.

Behavior Rating Inventory of Executive Function (BRIEF). The Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000) consists of two forms, a parent questionnaire and a teacher questionnaire. Each form consists of 86 items scored on a 3-point scale (Never, Sometimes, Often). It takes approximately 10 to 15 minutes to complete and can be used with children ages 5 to 18 years. The BRIEF assess eight subdomains of executive function: inhibition, shifting, and emotional control, which together comprise a broader composite score called the Behavioral Regulation Index (BRI), and initiation, working memory, planning/organizing, organization of materials, and monitoring, which together comprise the Metacognition Index (MI) composite. The BRI and MI are then combined to produce the overall Global Executive Composite (GEC) score. For this study, the BRI from the parent form of the BRIEF was used as a measure of behavioral regulation as reported by parents and the MI from the parent form of the BRIEF was used as a measure of metacognition as reported by parents. The parent form of the BRIEF was standardized on a sample of 1,419 parents from urban, suburban, and rural areas of Maryland. The sample was representative of 1999 U.S. Census data in regards to gender, socioeconomic status, ethnicity, age, and geographical population density. The reported Cronbach's α for the BRI on the Parent Form of the BRIEF is .94 and the reported test-retest reliability for the BRI is .84. The reported Cronbach's α for the MI on the Parent Form of the BRIEF is .96 and the reported test-retest reliability for the MI is .88.

Family functioning measure.

Family Assessment Device (FAD). Family functioning was measured using the Family Assessment Device (FAD), a well-established self-report measure of family functioning based upon the McMaster Model of Family Functioning (MMFF). It consists of six scales representing the six dimensions of family functioning included in the MMFF, as well as a General Functioning Scale (GFS) that provides a measure of overall family functioning based upon the other six scales. The FAD consists of 60 items about families and asks the rater to indicate how much each item describe their family's functioning on a 4-point Likert scale that ranges from strongly agree to strongly disagree. The FAD takes approximately 20 minutes to complete and can be administered to any family member over the age of 12. Higher scores on the scales of the FAD indicate higher levels of family dysfunction. It was administered to one adult from each family participating in the study. For the purposes of this study, the FAD GFS was used as a measure of overall family functioning. Kabacoff and colleagues conducted a study of the psychometric properties of the FAD among nonclinical (n = 627), psychiatric (n = 1,138) and medical (n = 298) samples (Kabacoff, Miller, Bishop, Epstein, & Keitner, 1990). Cronbach alphas for the GFS among these samples were .83, .84, and .86, respectively.

Socioeconomic status.

Socioeconomic status (SES) was determined for each patient using the median household income for the zip code in which they resided at the time of the study (U.S. Census Bureau, 2009-2013 5-Year American Community). These were then grouped into two groups: lower than the national median household income and higher than the median household income (Berkowitz, Traore, Singer, & Atlas, 2015).

Procedure

Approval by human subjects committee.

This study complied with ethical standards set forth by the American Psychological Association and the Institutional Review Board of the University of Texas at Austin. All research materials were approved prior to data collection by the Departmental Review Committee within the Department of Educational Psychology and by the Institutional Review Board (IRB) of The University of Texas at Austin. Each parent/guardian signed an IRB-approved consent form for their own participation as well as an IRB-approved form giving permission for their child to participate. Each youth participant signed a form of assent. The consent form can be found in Appendix A, the parent permission form can be found in Appendix B, and the youth assent form can be found in Appendix C.

In addition, IRB approval was obtained to access an archival neuropsychological dataset of childhood cancer survivors who participated in a larger, ongoing study of cognitive remediation and cognitive skills training funded by the Hyundai Hope on Wheels Foundation.

Recruitment of participants.

Participants for the experimental group were recruited through the Survivorship Center at the CBCC at DCMC and the Texas Child Study Center (TCSC) Embedded Clinic within the CBCC. Children who had been designated by their treatment team at the CBCC as survivors of pediatric ALL and who met the inclusion criteria were invited to participate in the study. Recruitment of experimental participants occurred in one of two ways. First of all, at the end of a regularly scheduled medical clinic or embedded clinic visit, a clinic staff member gave prospective youth and parent/guardian participants a

flyer that described the study and eligibility criteria for inclusion. Potential parent/guardian participants notified the clinic staff worker if they were willing to be contacted by the primary investigator to learn more. The clinic worker then obtained verbal consent to release parent/guardian and child name and contact information to the primary investigator. Secondly, potential experimental group participants who were not scheduled for a medical or embedded clinic visit during the recruitment period of the study were contacted by the primary investigator via phone and invited to participate. In total, 24 individuals were identified through the CBCC that met study criteria and were subsequently given flyers or contacted by the primary investigator. Five of these individuals ultimately declined to participate, five were non-responsive to the investigator's contact, three agreed to participate and scheduled appointments but then cancelled and were unable to be rescheduled, and one was excluded because he was overdue for a full neuropsychological evaluation. In addition, archival neuropsychological data for 10 childhood cancer survivors was obtained from the larger study mentioned above. Therefore, the total number of experimental group participants in the study was 20 caregiver/child dyads.

Control participants were recruited through community advertisements. IRB-approved advertisements were distributed to neighborhood, church, and school-related listserves. The advertisements contained contact information for the primary investigator and people interested in participating were asked to contact the primary investigator. In total, 23 individuals contacted the primary investigator. Three individuals ultimately declined to participate. Therefore, the total number of control group participants in the study was 20 caregiver/child dyads.

Consent.

Participation in the study was voluntary and participants were able to discontinue participation at any time, for any reason. Parent/guardian participants received a copy of the consent form and had the chance to discuss any concerns with the researcher. Youth participants were given a copy of the assent form and an opportunity to discuss any concerns with the researcher.

Data collection.

Children who assented to participate in the study, whose parents/guardians gave consent for participation, and who met inclusion criteria were participants. Once informed consent and assent were obtained, the parent or guardian of the child scheduled an appointment with the principal investigator for the child to participate in a neuropsychological evaluation. Children in the survivorship group who were due for their initial neuropsychological evaluation upon entering survivorship or those who were due for a neuropsychological re-evaluation took part in the full neuropsychological evaluation given as part of their routine clinical care. The measures used as part of the current study were administered as part of these full neuropsychological evaluations. Control participants and those survivors not due for evaluation or re-evaluation were administered a short neuropsychological battery comprised only of the measures being used as part of this investigation.

Evaluations of experimental group participants took place in a quiet, private room either at the CBCC in the Specially for Children building at DCMC in Austin, Texas (n = 14) or at the participant's home (n = 6). Control participants' evaluations took place in a quiet, private room either in the Sanchez Building at the University of Texas at Austin (n = 4) or at the participant's home (n = 16). Parents of participants in both groups were provided with a quiet, private room in which to complete their measures. The children

engaged in a one-on-one neuropsychological evaluation with the principal investigator for approximately 60 minutes (research-only battery) or 330 minutes (full battery) while their parent/guardian completed parent forms (BRIEF, BASC, FAD). The children were allowed to take breaks as needed during the testing session.

Chapter 4: Results

The purpose of this study was to examine the relations between family functioning and concurrent neurocognitive functioning among survivors of ALL treated with chemotherapy as opposed to a group of healthy controls. All statistical analyses were performed using SPSS (version 23.0).

Preliminary Data Analysis

Descriptive statistics.

Demographic characteristics of the sample are presented in Table 1. Means, standard deviations, and ranges for the FAD GFS and all outcome variables are reported in Table 2. As part of initial data cleaning, two outliers were identified. These will be described in more detail below. Means, standard deviations, and ranges for variables of interest with outliers removed are reported in Table 3. Demographic characteristics of the sample without the outliers are presented in Table 4. A correlation coefficient matrix was completed to determine correlations between FAD GFS and all variables of interest, including group membership, gender, SES, age at diagnosis, time since treatment, and all outcome variables. The correlation matrix of all variables with outliers included is displayed in Table 5. The correlation matrix of all variables without outliers is in Table 6.

Table 1.

Sample Demographic Characteristics.

		Clinical Group		Control Group		Total Group	
		Count	%	Count	%	Count	%
SES	Lower SES	7	35.0%	4	20.0%	11	27.5%
	Higher SES	13	65.0%	16	80.0%	29	72.5%
Gender	Male	12	60.0%	8	40.0%	20	50.0%
	Female	8	40.0%	12	60.0%	20	50.0%

Table 2.

Sample Performance on Outcome Measures

	Clinical Group (*n* = 20)		Control Group (*n* = 20)		Total Sample (*N* = 40)	
	M (SD)	Range	*M (SD)*	Range	*M (SD)*	Range
Sky Search[a]	8.95 (3.00)	2-16	9.90 (1.97)	7-13	9.42 (2.55)	2-16
Sky Search DT[a]	6.10 (3.97)	1-12	8.20 (3.78)	1-19	7.15 (3.97)	1-19
Score![a]	8.00 (3.39)	1-14	10.25 (3.01)	3-15	9.13 (3.36)	1-15
Creature Counting[a]	8.20 (3.22)	3-14	10.55 (2.33)	6-14	9.37 (3.02)	3-14
Attention Problems[b]	54.65 (10.49)	35-73	46.00 (7.95)	35-61	50.33 (10.18)	35-73
Working Memory Index[c]	93.45 (15.22)	68-129	103.90 (10.62)	88-126	98.67 (13.99)	68-129
Tower[a]	10.00 (2.13)	7-14	10.65 (2.13)	8-16	10.33 (2.13)	7-16
Inhibition[a]	9.90 (3.54)	1-15	10.25 (2.69)	4-14	10.07 (3.11)	1-15
Processing Speed Index[c]	91.75 (15.94)	59-115	104.20 (10.77)	85-121	97.98 (14.83)	59-121
Behavioral Regulation Index[b]	52.20 (8.85)	37-76	45.35 (6.24)	35-59	48.78 (8.32)	35-76
Metacognition Index[b]	57.05 (10.99)	37-77	47.50 (8.99)	35-67	52.27 (11.03)	35-77
FAD GFS[d]	1.86 (0.58)	1.00-3.42	1.49 (0.27)	1.00-1.92	1.67 (0.48)	1.00-3.42

[a] Sky Search, Score!, Creature Counting, Sky Search DT, Inhibition, and Tower: scores are scaled scores, with a mean of 10 and a standard deviation of 3. Higher scores indicate better performance. [b] Attention Problems, Behavioral Regulation Index, and Metacognition Index: scores are T-scores, with a mean of 50 and a standard deviation of 10. Higher scores indicate more difficulties in that domain. [c] Working Memory Index, Processing Speed Index: scores are standard scores, with a mean of 100 and a standard deviation of 15. Higher scores indicate better performance. [d] Family Assessment Device (FAD) General Functioning Scale (GFS): higher scores indicate more difficulties with family functioning.

Table 3.

Sample Performance on Outcome Measures without Outliers

	Clinical Group (n = 18)		Control Group (n = 20)		Total Sample (N = 38)	
	M (SD)	Range	*M (SD)*	Range	*M (SD)*	Range
Sky Search[a]	8.50 (2.62)	2-13	9.90 (1.97)	7-13	9.24 (2.38)	2-13
Sky Search DT[a]	6.06 (4.17)	1-12	8.20 (3.78)	1-19	7.18 (4.06)	1-19
Score![a]	8.22 (3.49)	1-14	10.25 (3.01)	3-15	9.29 (3.36)	1-15
Creature Counting[a]	8.28 (3.39)	3-14	10.55 (2.33)	6-14	9.47 (3.07)	3-14
Attention Problems[b]	52.78 (9.26)	35-70	46.00 (7.95)	35-61	49.21 (9.14)	35-70
Working Memory Index[c]	94.06 (15.97)	68-129	103.90 (10.62)	88-126	99.24 (14.14)	68-129
Tower[a]	10.11 (2.22)	7-14	10.65 (2.13)	8-16	10.39 (2.16)	7-16
Inhibition[a]	10.17 (3.54)	1-15	10.25 (2.69)	4-14	10.21 (3.08)	1-15
Processing Speed Index[c]	92.56 (16.33)	59-115	104.20 (10.77)	85-121	98.68 (14.72)	59-121
Behavioral Regulation Index[b]	51.33 (7.04)	37-62	45.35 (6.24)	35-59	48.18 (7.20)	35-62
Metacognition Index[b]	55.11 (9.72)	37-73	47.50 (8.99)	35-67	51.11 (9.99)	35-73
FAD GFS[d]	1.77 (.47)	1.00-2.75	1.49 (0.27)	1.00-1.92	1.62 (.40)	1.00-2.75

[a] Sky Search, Score!, Creature Counting, Sky Search DT, Inhibition, and Tower: scores are scaled scores, with a mean of 10 and a standard deviation of 3. Higher scores indicate better performance. [b] Attention Problems, Behavioral Regulation Index, and Metacognition Index: scores are T-scores, with a mean of 50 and a standard deviation of 10. Higher scores indicate more difficulties in that domain. [c] Working Memory Index, Processing Speed Index: scores are standard scores, with a mean of 100 and a standard deviation of 15. Higher scores indicate better performance. [d] Family Assessment Device (FAD) General Functioning Scale (GFS): higher scores indicate more difficulties with family functioning.

Table 4.

Sample Demographic Characteristics without Outliers

		Clinical Group		Control Group		Total Group	
		Count	%	Count	%	Count	%
SES	Lower SES	7	38.9%	4	20.0%	11	28.9%
	Higher SES	11	61.1%	16	80.0%	27	71.1%
Gender	Male	10	55.6%	8	40.0%	18	47.4%
	Female	8	44.4%	12	60.0%	20	52.6%

Assumptions for statistics used in main analyses.

The data were examined for violation of assumptions required for multiple regression statistical procedures. Data were checked for outliers. As mentioned above, two outliers were identified. One participant's score on the Behavioral Regulation Index was 3.27 standard deviations above the mean. A different participant's score on the FAD GFS was 3.64 standard deviations above the mean. Analyses were conducted with and without these participants included and results for each are presented below. Analyses were also conducted with the outliers transformed (Behavioral Regulation Index was transformed with a square root transformation and FAD GFS was transformed with a log10 transformation). The results of the analyses using the transformed variables were consistent with the results of the analyses using the variables without transformation. The results using the variables without transformations are presented below.

Normal distribution of residuals was confirmed using a p-p plot of observed and expected values. Residual scatterplots revealed that the assumptions of normality, linearity, and homoscedasticity were all satisfied. The independence of residuals was confirmed using the Durbin-Watson test. Data also met the assumption of multicollinearity, as confirmed with collinearity statistics (i.e., Tolerance and VIF) that were all within accepted limits.

Table 5.

Correlations Among Variables of Interest in Sample

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.
1. Group Membership	-																
2. Gender	-.200	-															
3. SES	-.168	-.056	-														
4. Age at Dx	.a	.284	-.136	-													
5. Time Since Tx	.a	-.141	.180	-.427	-												
6. Sky Search	-.189	-.050	.482**	-.404	.493*	-											
7. Score!	-.339*	.158	.259	.279	-.393	-.150	-										
8. Creature Counting	-.394*	.075	.397*	.553*	-.176	.032	.627**	-									
9. Sky Search DT	-.268	.000	.423**	.197	-.121	.032	.469**	.566**	-								
10. Atten Problems	.430**	-.306	.243	-.076	.402	.058	-.244	-.021	.105	-							
11. WMI	-.378*	-.139	.216	.198	-.203	.122	.428**	.538**	.487**	-.214	-						
12. PSI	-.425**	.189	.439**	-.096	-.110	.496**	.420**	.495**	.438**	-.401*	.680**	-					
13. Inhib.	-.057	-.024	.197	.244	-.213	.174	.254	.333*	.371*	-.209	.365*	.541**	-				
14. Tower	-.155	.059	.015	.465*	-.178	-.092	-.027	.364*	.252	-.089	.113	.110	.287	-			
15. BRI	.417**	-.277	-.065	-.172	.129	-.153	-.389*	-.364*	-.062	.644**	-.252	-.432**	-.156	-.154	-		
16. MI	.438**	-.273	.211	-.126	.534*	.116	-.372*	-.155	.036	.879**	-.179	-.368*	-.235	-.091	.735**	-	
17. FAD GF	.389*	-.214	.194	-.131	.318	.142	-.038	-.067	.039	.631**	-.228	-.182	.010	-.238	.316*	.571**	-

Note: *$p < .05$, **$p < .01$, a. cannot be computed because at least one of the variables is constant and this variable is only relevant for the clinical sample.

Table 6.

Correlations Among Variables of Interest in Sample Without Outliers

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.
1. Group Membership	-																
2. Gender	-.156	-															
3. SES	-.208	-.024	-														
4. Age at Dx	.a	.239	-.086	-													
5. Time Since Tx	.a	.011	.060	-.382	-												
6. Sky Search	-.298	.028	.485**	-.359	.236	-											
7. Score!	-.305	.115	.301	.251	-.397	-.110	-										
8. Creature Counting	-.375*	.044	.426**	.555*	-.188	.077	.616**	-									
9. Sky Search DT	-.267	-.009	.435**	.207	-.136	.074	.481**	.573**	-								
10. Atten Problems	.375*	-.229	.201	.053	.172	-.114	-.161	.058	.139	-							
11. WMI	-.352*	-.188	.248	.177	-.172	.202	.407*	.526**	.490**	-.149	-						
12. PSI	-.400*	.150	.489**	-.130	-.099	.600**	.387*	.480**	.460**	-.347*	.675**	-					
13. Inhib.	-.014	-.073	.235	.219	-.196	.215	.214	.313	.395*	-.130	.349*	.508**	-				
14. Tower	-.126	.027-	.036	.447	-.115	-.050	-.061	.350*	.250	-.022	.090	.083	.271	-			
15. BRI	.420**	.250	-.130	-.176	.202	-.181	-.355*	-.363*	-.104	.648**	-.237	-.371*	-.020	-.130	-		
16. MI	.386*	-.193	.166	-.012	.386	-.028	-.311	-.098	.056	.844**	-.110	-.307	-.160	-.027	.761**	-	
17. FAD GF	.362*	-.138	.162	-.017	-.083	-.147	.046	-.019	.111	.598**	-.185	-.179	.039	-.215	.494**	.528**	-

Note: * $p < .05$, ** $p < .01$, a. cannot be computed because at least one of the variables is constant and this variable is only relevant for the clinical sample.

Main Analyses

Hierarchical multiple regression analyses were conducted to examine the relations between family functioning and multiple measures of neurocognitive functioning. First, a test for interaction effects was performed to see if the magnitude of the effect of group membership (survivor vs. healthy control) on neurocognitive functioning varies as a function of family functioning. The *p*-value associated with the change in R^2 was examined to see if family functioning moderated the effect of group membership on neurocognitive functioning. A change in R^2 associated with an alpha of less than .05 was considered significant.

Hypothesis 1a.

Family functioning was expected to moderate the impact of group membership (survivor vs. healthy control) on performance on a task of selective attention. Furthermore, family functioning was expected to explain a significant amount of variance in performance on a task of selective attention, above and beyond that accounted for by demographic and treatment-related variables in the ALL group. In the control group, family functioning was not expected to account for a significant amount of additional variance in performance on a task of selective attention beyond that accounted for by demographic variables.

In order to test for an interaction between group and family functioning on selective attention, a hierarchical regression analysis was performed. Results are presented in Table 7. Selective attention (the attention scaled score on Sky Search) was regressed on Group (survivor or healthy control) and family functioning (FAD_GF_Centered) using simultaneous multiple regression. These two variables accounted for 9.0% of the variance in selective attention on Sky Search (F [2, 37] =

1.840, p = .173). Neither group membership (b = -.288, t [38] = -1.689, p = .100) nor family functioning (b = .254, t [38] = 1.494, p = .144) by themselves had a significant effect on selective attention.

The interaction term (Group_FAD_GF_Centered) was added to the equation in the second step of the hierarchical regression. The addition of the interaction term did not lead to a statistically significant increase in R^2 (ΔR^2 = .024, F [1, 36] = .996, p = .325). Thus, this regression analysis indicated that family functioning did not moderate the impact of group membership on performance on a task of selective attention with outliers included in the analysis.

Table 7.

Selective Attention (With Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.090	.090
Constant	10.092	.573			
Group membership	-1.448	.857	-.288		
Family functioning	1.350	.903	.254		
Step 2				.115	.024
Constant	9.815	.637			
Group membership	-.596	2.149	-.112		
Family functioning	-1.266	.877	-.251		
Group X Family functioning	2.363	2.368	.387		

Note. N = 40; * p < .05, ** p < .01, *** p < .001

The analysis was conducted again with the outliers removed. Results are presented in Table 8. In step one, group membership and family functioning accounted for 9.1% of the variance in selective attention (F [2, 35] = 1.745, p = .190). Neither group membership (b = -.282, t [36] = -1.630, p = .112) nor family functioning (b = -.045, t [36] = -.260, p = .796) by themselves had a significant effect on selective attention. In step two, the addition of the interaction term did not lead to a statistically significant increase

in R^2 (ΔR^2 = .001, F [1, 34] = .035, p = .852). Therefore, family functioning did not moderate the impact of group membership on performance on a task of selective attention with or without the outliers removed from analyses. Because the interaction term was not statistically significant the planned follow-up analysis testing the regression coefficients separately by group was not conducted.

Table 8.

Selective Attention (Without Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.091	.091
Constant	9.862	.541			
Group membership	-1.324	.812	-.282		
Family functioning	-.269	1.035	-.045		
Step 2				.092	.001
Constant	9.815	.602			
Group membership	-1.294	.838	-.276		
Family functioning	-.596	2.032	-.100		
Group X Family functioning	.445	2.373	.061		

Note. N = 38; * p < .05, ** p < .01, *** p < .001

Hypothesis 1b.

Family functioning was expected to moderate the impact of group membership (survivor vs. healthy control) on performance on a task of divided attention. Furthermore, family functioning was expected to explain a significant amount of variance in performance on a task of divided attention, above and beyond that accounted for by demographic and treatment-related variables in the ALL group. In the control group, family functioning was not expected to account for a significant amount of additional variance in performance on a task of divided attention beyond that accounted for by demographic variables.

A hierarchical regression analysis was performed in order to test for an interaction between group and family functioning on divided attention. Results are presented in Table 9. Divided attention (the scaled score on Sky Search DT) was regressed on Group (survivor or healthy control) and family functioning (FAD_GF_Centered) using simultaneous multiple regression. These two variables accounted for 9.6% of the variance in divided attention on Sky Search DT (F [2, 37] = 1.964, p = .155). Neither group membership (b = -.334, t [38] = -1.966, p = .057) nor family functioning (b = .169, t [38] = .997, p = .325) by themselves had a significant effect on divided attention.

The interaction term (Group_FAD_GF_Centered) was added to the equation in the second step of the hierarchical regression. The addition of the interaction term did not lead to a statistically significant increase in R^2 (ΔR^2 < .001, F [1, 36] = .019, p = .891). Therefore, family functioning did not moderate the impact of group membership on performance on a task of divided attention with outliers included in the analysis.

Table 9.

Divided Attention (With Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.096	.096
Constant	8.399	.890			
Group membership	-2.616	1.331	-.334		
Family functioning	1.398	1.402	.169		
Step 2				.096	.000
Constant	8.459	1.002			
Group membership	-2.656	1.379	-.339		
Family functioning	1.821	3.380	.220		
Group X Family functioning	-.514	3.725	-.054		

Note. N = 40; * p < .05, ** p < .01, *** p < .001

The analysis was conducted again with the outliers removed. Results are presented in Table 10. In step one, group membership and family functioning accounted

for 12.1% of the variance in divided attention (F [2, 35] = 2.412, p = .104). By itself, group membership had a significant effect on divided attention (b = -.354, t [36] = -2.081, p = .045). However, family functioning did not have a significant independent effect on divided attention (b = .239, t [36] = 1.406, p = .168). In step two, the addition of the interaction term did not lead to a statistically significant increase in R^2 (ΔR^2 = .001, F [1, 34] = .045, p = .832). Family functioning did not moderate the impact of group membership on performance on a task of divided attention with or without the outliers removed from analyses. Because the interaction term was not statistically significant the follow-up analysis testing the regression coefficients separately by group was not conducted.

Table 10.

Divided Attention (Without Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.121	.121
Constant	8.548	.909			
Group membership	-2.838	1.364	-.354*		
Family functioning	2.444	1.738	.239		
Step 2				.122	.001
Constant	8.459	1.012			
Group membership	-2.781	1.408	-.347		
Family functioning	1.821	3.413	.178		
Group X Family functioning	.849	3.985	.068		

Note. N = 38; * p < .05, ** p < .01, *** p < .001

Hypothesis 1c.

Family functioning was expected to moderate the impact of group membership (survivor vs. healthy control) on performance on a task of sustained attention. Furthermore, family functioning was expected to explain a significant amount of variance in performance on a task of sustained attention, above and beyond that accounted for by

demographic and treatment-related variables in the ALL group. In the control group, family functioning was not expected to account for a significant amount of additional variance in performance on a task of sustained attention beyond that accounted for by demographic variables.

In order to test for an interaction between group and family functioning on sustained attention, a hierarchical regression analysis was performed. Results are presented in Table 11. Sustained attention (the scaled score on the Score! subtest of the TEA-Ch) was regressed on Group (survivor or healthy control) and family functioning (FAD_GF_Centered) using simultaneous multiple regression. These two variables accounted for 12.5% of the variance in sustained attention on Score! (F [2, 37] = 2.652, p = .084). By itself, group membership had a significant effect on sustained attention (b = -382, t [38] = -2.290, p = .028). However, family functioning did not have a significant independent effect on sustained attention (b = .111, t [38] = .664, p = .511).

Table 11.

Sustained Attention (With Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.125	.125
Constant	10.360	.740			
Group membership	-2.536	1.108	-.382*		
Family functioning	.775	1.167	.111		
Step 2				.129	.004
Constant	10.219	.832			
Group membership	-2.443	1.146	-.368*		
Family functioning	-.220	2.808	-.031		
Group X Family functioning	1.209	3.095	.150		

Note. N = 40; * p < .05, ** p < .01, *** p < .001

The interaction term (Group_FAD_GF_Centered) was added to the equation in the second step of the hierarchical regression. The addition of the interaction term did not

lead to a statistically significant increase in R^2 (ΔR^2 = .004, F [1, 36] = .152, p = .698). Family functioning did not moderate the impact of group membership on performance on a task of sustained attention with outliers included in the analysis.

The analysis was conducted again with the outliers removed. Results are presented in Table 12. In step one, group membership and family functioning accounted for 12.2% of the variance in sustained attention (F [2, 35] = 2.422, p = .103). By itself, group membership had a significant effect on sustained attention (b = -.371, t [36] = -2.181, p = .036). However, family functioning did not have a significant independent effect on sustained attention (b = .181, t [36] = 1.063, p = .295). In step two, the addition of the interaction term did not lead to a statistically significant increase in R^2 (ΔR^2 = .013, F [1, 34] = .530, p = .472). Therefore, family functioning did not moderate the impact of group membership on performance on a task of sustained attention with or without outliers removed. Because the interaction term was not statistically significant the follow-up analysis testing the regression coefficients separately by group was not conducted.

Table 12.

Sustained Attention (Without Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.122	.122
Constant	10.468	.753			
Group membership	-2.462	1.129	-.371*		
Family functioning	1.528	1.438	.181		
Step 2				.135	.013
Constant	10.219	.831			
Group membership	-2.302	1.157	-3.47		
Family functioning	-.220	2.805	-.026		
Group X Family functioning	2.384	3.275	.231		

Note. N = 38; * p < .05, ** p < .01, *** p < .001

Hypothesis 1d.

Family functioning was expected to moderate the impact of group membership (survivor vs. healthy control) on performance on a task of switching attention. Furthermore, family functioning was expected to explain a significant amount of variance in performance on a task of switching attention, above and beyond that accounted for by demographic and treatment-related variables in the ALL group. In the control group, family functioning was not expected to account for a significant amount of additional variance in performance on a task of switching attention beyond that accounted for by demographic variables.

In order to test for an interaction between group and family functioning on switching attention, a hierarchical regression analysis was performed. Results are presented in Table 13. Switching attention (the accuracy score on the Creature Counting subtest on the TEA-Ch) was regressed on group membership (survivor or healthy control) and family functioning (FAD_GF_Centered) using simultaneous multiple regression.

These two variables accounted for 16.4% of the variance in switching attention on

Table 13.

Switching Attention (With Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.164*	.164*
Constant	10.641	.650			
Group membership	-2.585	.973	-.434*		
Family functioning	.636	1.025	.101		
Step 2				.170	.006
Constant	10.804	.730			
Group membership	-2.692	1.005	-.452*		
Family functioning	1.782	2.462	.284		
Group X Family functioning	-1.392	2.714	-.193		

Note. $N = 40$; * $p < .05$, ** $p < .01$, *** $p < .001$

Creature Counting (F [2, 37] = 3.632, p = .036). By itself, group membership had a significant effect on switching attention (b = -.434, t [38] = -2.658, p = .012), such that the control group scored higher than the clinical group. However, family functioning did not have a significant independent effect on switching attention (b = .101, t [38] = .621, p = .539).

The interaction term (Group_FAD_GF_Centered) was added to the equation in the second step of the hierarchical regression. The addition of the interaction term did not lead to a statistically significant increase in R^2 (ΔR^2 = .006, F [1, 36] = .263, p = .611). Family functioning did not moderate the impact of group membership on performance on a task of switching attention with outliers included in the analysis.

The analysis was conducted again with the outliers removed. Results are presented in Table 14. In step one, group membership and family functioning accounted for 15.6% of the variance in switching attention (F [2, 35] = 3.247, p = .051). By itself, group membership had a significant effect on switching attention (b = -.424, t [36] = -2.545, p = .015). However, family functioning did not have a significant independent effect on switching attention (b = .135, t [36] = .808, p = .425). In step two, the addition

Table 14.

Switching Attention (Without Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.156	.156
Constant	10.698	.672			
Group membership	-2.567	1.008	-.424*		
Family functioning	1.038	1.285	.135		
Step 2				.159	.003
Constant	10.804	.747			
Group membership	-2.635	1.040	-.435*		
Family functioning	1.782	2.521	.231		
Group X Family functioning	-1.014	2.944	-.108		

Note. $N = 38$; * $p < .05$, ** $p < .01$, *** $p < .001$

of the interaction term did not lead to a statistically significant increase in R^2 ($\Delta R^2 = .003$, F [1, 34] = .119, $p = .733$). Thus, family functioning did not moderate the impact of group membership on performance on a task of switching attention with or without outliers removed. Because the interaction term was not statistically significant the follow-up analysis testing the regression coefficients separately by group was not conducted.

Hypothesis 1e.

Family functioning was expected to moderate the impact of group membership (survivor vs. healthy control) on scores on caregiver ratings of attention. Furthermore, family functioning was expected to explain a significant amount of variance in scores on caregiver ratings of attention, above and beyond that accounted for by demographic and treatment-related variables in the ALL group. In the control group, family functioning was not expected to account for a significant amount of additional variance in scores on caregiver ratings of attention beyond that accounted for by demographic variables.

In order to test for an interaction between group and family functioning on caregiver ratings of attention, a hierarchical regression analysis was performed. Results are presented in Table 15. Caregiver ratings of attention (the Attention Problems T-score on the Parent Form of the BASC) was regressed on Group (survivor or healthy control) and family functioning (FAD_GF_Centered) using simultaneous multiple regression. These two variables accounted for 43.9% of the variance in caregiver ratings of attention on the BASC (F [2, 37] = 14.463, $p < .001$). By itself, group membership did not have a significant effect on caregiver ratings of attention ($b = .218$, t [38] = 1.628, $p = .112$). However, family functioning did have a significant independent effect on caregiver ratings of attention ($b = .547$, t [38] = 4.089, $p < .001$).

The interaction term (Group_FAD_GF_Centered) was added to the equation in the second step of the hierarchical regression. The addition of the interaction term did not lead to a statistically significant increase in R^2 (ΔR^2 = .006, F [1, 36] = .377, p = .543). Thus, this regression analysis indicated that family functioning did not moderate the impact of group membership on performance on caregiver ratings of attention with outliers included in the analysis.

Table 15.

Caregiver Ratings of Attention (With Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.439***	.439***
Constant	47.650	1.797			
Group membership	4.375	2.687	.218		
Family functioning	11.577	2.831	.547***		
Step 2				.445	.006
Constant	47.111	2.013			
Group membership	4.730	2.771	.235		
Family functioning	7.793	6.793	.368		
Group X Family functioning	4.596	7.486	.189		

Note. N = 40; * p < .05, ** p < .01, *** p < .001

The analysis was conducted again with the outliers removed. Results are presented in Table 16. In step one, group membership and family functioning accounted for 38.7% of the variance in parent ratings of attention (F [2, 35] = 11.047, p < .001). By itself, group membership did not have a significant effect on parent ratings of attention (b = .183, t [36] = 1.286, p = .207). However, family functioning did have a significant independent effect on parent ratings of attention (b = .532, t [36] = 3.749, p = .001). In step two, the addition of the interaction term did not lead to a statistically significant increase in R^2 (ΔR^2 = .012, F [1, 34] = .671, p = .419). The regression analysis indicated that family functioning did not moderate the impact of group membership on

performance on parent ratings of attention with or without outliers removed. Because the interaction term was not statistically significant the follow-up analysis testing the regression coefficients separately by group was not conducted.

Table 16.

Caregiver Ratings of Attention (Without Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.387	.387
Constant	47.746	1.710			
Group membership	3.299	2.565	.183		
Family functioning	12.255	3.269	.532***		
Step 2				.399	.012
Constant	47.111	1.886			
Group membership	3.705	2.624	.205		
Family functioning	7.793	6.361	.338		
Group X Family functioning	6.083	7.428	.216		

Note. $N = 38$; * $p < .05$, ** $p < .01$, *** $p < .001$

Hypothesis 2a.

Family functioning was expected to moderate the impact of group membership (survivor vs. healthy control) on performance on a task of cognitive flexibility (working memory). Furthermore, family functioning was expected to explain a significant amount of variance in performance on a task of cognitive flexibility (working memory), above and beyond that accounted for by demographic and treatment-related variables in the ALL group. In the control group, family functioning was not expected to account for a significant amount of additional variance in performance on a task of cognitive flexibility (working memory) beyond that accounted for by demographic variables.

In order to test for an interaction between group and family functioning on cognitive flexibility (working memory), a hierarchical regression analysis was performed. Results are presented in Table 17. Cognitive flexibility (the Working Memory Index

score on the WISC-IV) was regressed on Group (survivor or healthy control) and family functioning (FAD_GF_Centered) using simultaneous multiple regression. These two variables accounted for 15.1% of the variance in cognitive flexibility (working memory) on the Working Memory Index (F [2, 37] = 3.282, p = .049). By itself, group membership had a significant effect on cognitive flexibility (b = -.341, t [38] = -2.074, p = .045). However, family functioning did not have a significant independent effect on cognitive flexibility (b = -.095, t [38] = -.578, p = .567).

The interaction term (Group_FAD_GF_Centered) was added to the equation in the second step of the hierarchical regression. The addition of the interaction term did not lead to a statistically significant increase in R^2 (ΔR^2 = .001, F [1, 36] = .058, p = .812). Therefore, family functioning did not moderate the impact of group membership on performance on a task of cognitive flexibility (working memory) with outliers included in the analysis.

Table 17.

Cognitive Flexibility: Working Memory (With Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.151*	.151*
Constant	103.505	3.038			
Group membership	-9.427	4.545	-.341*		
Family functioning	-2.770	4.788	-.095		
Step 2				.152	.001
Constant	103.148	3.420			
Group membership	-9.192	4.708	-.333		
Family functioning	-5.281	11.538	-.181		
Group X Family functioning	3.050	12.716	.091		

Note. N = 40; * p < .05, ** p < .01, *** p < .001

The analysis was conducted again with the outliers removed. Results are presented in Table 18. In step one, group membership and family functioning accounted

for 12.8% of the variance in cognitive flexibility (F [2, 35] = 2.566, p = .091). Neither group membership (b = -.329, t [36] = -1.940, p = .060) nor family functioning (b = -.066, t [36] = -.388, p = .700) by themselves had a significant effect on cognitive flexibility (working memory). In step two, the addition of the interaction term did not lead to a statistically significant increase in R^2 (ΔR^2 = .002, F [1, 34] = .084, p = .774). Thus, this regression analysis indicated that family functioning did not moderate the impact of group membership on performance on a task of cognitive flexibility (working memory) with or without outliers removed. Because the interaction term was not statistically significant the follow-up analysis testing the regression coefficients separately by group was not conducted.

Table 18.

Cognitive Flexibility: Working Memory (Without Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.128	.128
Constant	103.566	3.155			
Group membership	-9.180	4.731	-.329		
Family functioning	-2.341	6.029	-.066		
Step 2				.130	.002
Constant	103.148	3.508			
Group membership	-8.912	4.883	-.319		
Family functioning	-5.281	11.835	-.148		
Group X Family functioning	4.007	13.819	.092		

Note. N = 38; * p < .05, ** p < .01, *** p < .001

Hypothesis 2b.

Family functioning was expected to moderate the impact of group membership (survivor vs. healthy control) on performance on a task of goal setting (planning). Furthermore, family functioning was expected to explain a significant amount of variance in performance on a task of goal setting (planning), above and beyond that accounted for

by demographic and treatment-related variables in the ALL group. In the control group, family functioning was not expected to account for a significant amount of additional variance in performance on a task of goal setting (planning) beyond that accounted for by demographic variables.

In order to test for an interaction between group and family functioning on goal setting (planning), a hierarchical regression analysis was performed. Results are presented in Table 19. Goal setting (the total achievement scaled score on the Tower subtest of the D-KEFS) was regressed on Group (survivor or healthy control) and family functioning (FAD_GF_Centered) using simultaneous multiple regression. These two variables accounted for 6.1% of the variance in goal setting (planning) on the Tower subtest (F [2, 37] = 1.207, p = .311). Neither group membership (b = -.073, t [38] = -.422, p = .675) nor family functioning (b = -.210, t [38] = -1.213, p = .233) by themselves had a significant effect on goal setting (planning).

Table 19.

Goal Setting: Planning (With Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.061	.061
Constant	10.518	.486			
Group membership	-.307	.727	-.073		
Family functioning	-.929	.766	-.210		
Step 2				.063	.002
Constant	10.587	.547			
Group membership	-.353	.753	-.084		
Family functioning	-.442	1.845	-.100		
Group X Family functioning	-.591	2.033	-.116		

Note. N = 40; * p < .05, ** p < .01, *** p < .001

The interaction term (Group_FAD_GF_Centered) was added to the equation in the second step of the hierarchical regression. The addition of the interaction term did not

lead to a statistically significant increase in R^2 (ΔR^2 = .002, F [1, 36] = .085, p = .773). Family functioning did not moderate the impact of group membership on performance on a task of goal setting (planning) with outliers included in the analysis.

The analysis was conducted again with the outliers removed. Results are presented in Table 20. In step one, group membership and family functioning accounted for 4.9% of the variance in goal setting (F [2, 35] = .903, p = .415). Neither group membership (b = -.055, t [36] = -.313, p = .756) nor family functioning (b = -.195, t [36] = -1.105, p = .277) by themselves had a significant effect on goal setting. In step two, the addition of the interaction term did not lead to a statistically significant increase in R^2 (ΔR^2 = .004, F [1, 34] = .148, p = .703). Family functioning did not moderate the impact of group membership on performance on a task of goal setting (planning) with or without outliers removed. Because the interaction term was not statistically significant the follow-up analysis testing the regression coefficients separately by group was not conducted.

Table 20.

Goal Setting: Planning (Without Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.049	.049
Constant	10.498	.504			
Group membership	-.237	.756	-.055		
Family functioning	-1.064	.963	-.195		
Step 2				.053	.004
Constant	10.587	.560			
Group membership	-.293	.779	-.069		
Family functioning	-.442	1.889	-.081		
Group X Family functioning	-.848	2.205	-.127		

Note. N = 38; * p < .05, ** p < .01, *** p < .001

Hypothesis 2c.

Family functioning was expected to moderate the impact of group membership (survivor vs. healthy control) on performance on a task of attentional control (inhibition). Furthermore, family functioning was expected to explain a significant amount of variance in performance on a task of attentional control (inhibition), above and beyond that accounted for by demographic and treatment-related variables in the ALL group. In the control group, family functioning was not expected to account for a significant amount of additional variance in performance on a task of attentional control (inhibition) beyond that accounted for by demographic variables.

In order to test for an interaction between group and family functioning on attentional control (inhibition), a hierarchical regression analysis was performed. Results are presented in Table 21. Attentional control (the Trial 3: Inhibition time scaled score on the D-KEFS Color-Word Interference Test) was regressed on Group (survivor or healthy control) and family functioning (FAD_GF_Centered) using simultaneous multiple regression. These two variables accounted for 0.4% of the variance in attentional control (inhibition) on Trial 3 of the D-KEFS Color-Word Interference Test (F [2, 37] = .083, p = .920). Neither group membership (b = -.072, t [38] = -.403, p = .689) nor family functioning (b = .038, t [38] = .214, p = .832) by themselves had a significant effect on attentional control (inhibition).

The interaction term (Group_FAD_GF_Centered) was added to the equation in the second step of the hierarchical regression. The addition of the interaction term did not lead to a statistically significant increase in R^2 (ΔR^2 = .007, F [1, 36] = .272, p = .605). Thus, this regression analysis indicated that family functioning did not moderate the impact of group membership on performance on a task of attentional control (inhibition) with outliers included in the analysis.

Table 21.

Attentional Control: Inhibition (With Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.004	.004
Constant	10.285	.731			
Group membership	-.441	1.093	-.072		
Family functioning	.246	1.151	.038		
Step 2				.012	.007
Constant	10.098	.820			
Group membership	-.318	1.129	-.052		
Family functioning	-1.064	2.766	-.165		
Group X Family functioning	1.591	3.049	.214		

Note. $N = 40$; * $p < .05$, ** $p < .01$, *** $p < .001$

The analysis was conducted again with the outliers removed. Results are presented in Table 22. In step one, group membership and family functioning accounted for 0.2% of the variance in attentional control (F [2, 35] = .043, p = .958). Neither group membership (b = -.032, t [36] = -.178, p = .860) nor family functioning (b = .051, t [36] = .282, p = .780) by themselves had a significant effect on attentional control (inhibition). In step two, the addition of the interaction term did not lead to a statistically significant increase in R^2 (ΔR^2 = .011, F [1, 34] = .386, p = .539). Family functioning did not

Table 22.

Attentional Control: Inhibition (Without Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.002	.002
Constant	10.306	.734			
Group membership	-.196	1.101	-.032		
Family functioning	.395	1.403	.051		
Step 2				.014	.011
Constant	10.098	.813			
Group membership	-.063	1.131	-.010		
Family functioning	-1.064	2.743	-.137		
Group X Family functioning	1.989	3.202	.210		

Note. $N = 38$; * $p < .05$, ** $p < .01$, *** $p < .001$

moderate the impact of group membership on performance on a task of attentional control (inhibition) with or without outliers removed. Because the interaction term was not statistically significant the follow-up analysis testing the regression coefficients separately by group was not conducted.

Hypothesis 2d.

Family functioning was expected to moderate the impact of group membership (survivor vs. healthy control) on performance on a task of information processing (processing speed). Furthermore, family functioning was expected to explain a significant amount of variance in performance on a task of information processing (processing speed), above and beyond that accounted for by demographic and treatment-related variables in the ALL group. In the control group, family functioning was not expected to account for a significant amount of additional variance in performance on a task of information processing (processing speed) beyond that accounted for by demographic variables.

In order to test for an interaction between group and family functioning on information processing (processing speed), a hierarchical regression analysis was performed. Results are presented in Table 23. Information processing (the Processing Speed Index score on the WISC-IV) was regressed on Group (survivor or healthy control) and family functioning (FAD_GF_Centered) using simultaneous multiple regression. These two variables accounted for 18.1% of the variance in information processing (processing speed) on the Processing Speed Index (F [2, 37] = 4.088, p = .025). By itself, group membership had a significant effect on information processing (b = -.417, t [38] = -2.584, p = .014). However, family functioning did not have a significant independent effect on information processing (b = -.020, t [38] = -.123, p = .903).

The interaction term (Group_FAD_GF_Centered) was added to the equation in the second step of the hierarchical regression. The addition of the interaction term did not lead to a statistically significant increase in R^2 (ΔR^2 = .000, F [1, 36] = .015, p = .903). Family functioning did not moderate the impact of group membership on performance on a task of information processing (processing speed) with outliers included in the analysis.

Table 23.

Information Processing: Processing Speed (With Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.181*	.181*
Constant	104.113	3.163			
Group membership	-12.224	4.731	-.417*		
Family functioning	-.613	4.984	-.020		
Step 2				.181	.000
Constant	103.922	3.562			
Group membership	-12.098	4.903	-.413*		
Family functioning	-1.954	12.018	-.063		
Group X Family functioning	1.629	13.245	.046		

Note. N = 40; * p < .05, ** p < .01, *** p < .001

The analysis was conducted again with the outliers removed. Results are presented in Table 24. In step one, group membership and family functioning accounted for 16.2% of the variance in information processing (F [2, 35] = 3.372, p = .046). By itself, group membership had a significant effect on information processing (b = -.386, t [36] = -2.325, p = .026). However, family functioning did not have a significant independent effect on information processing (b = -.039, t [36] = -.238, p = .814). In step two, the addition of the interaction term did not lead to a statistically significant increase in R^2 (ΔR^2 = .000, F [1, 34] = .002, p = .962). Thus, this regression analysis indicated that family functioning did not moderate the impact of group membership on performance on a task of information processing (processing speed) with or without outliers removed.

Because the interaction term was not statistically significant the follow-up analysis testing the regression coefficients separately by group was not conducted.

Table 24.

Information Processing: Processing Speed (Without Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.162*	.162*
Constant	103.992	3.221			
Group membership	-11.229	4.830	-.386*		
Family functioning	-1.462	6.155	-.039		
Step 2				.162	.000
Constant	103.922	3.586			
Group membership	-11.185	4.990	-.384*		
Family functioning	-1.954	12.097	-.053		
Group X Family functioning	.670	14.124	.015		

Note. $N = 38$; * $p < .05$, ** $p < .01$, *** $p < .001$

Hypothesis 2e.

Family functioning was expected to moderate the impact of group membership (survivor vs. healthy control) on scores on caregiver ratings of an aspect of executive functioning (behavioral regulation). Furthermore, family functioning was expected to explain a significant amount of variance in scores on caregiver ratings of behavioral regulation, above and beyond that accounted for by demographic and treatment-related variables in the ALL group. In the control group, family functioning was not expected to account for a significant amount of additional variance in scores on caregiver ratings of behavioral regulation beyond that accounted for by demographic variables.

In order to test for an interaction between group and family functioning on caregiver ratings of behavioral regulation, a hierarchical regression analysis was performed. Results are presented in Table 25. Caregiver ratings of behavioral regulation (the Behavioral Regulation Index score on the Parent Form of the BRIEF) was regressed

on Group (survivor or healthy control) and family functioning (FAD_GF_Centered) using simultaneous multiple regression. These two variables accounted for 20.2% of the variance in caregiver ratings of behavioral regulation on the Behavioral Regulation Index (F [2, 37] = 4.681, p = .015). By itself, group membership had a significant effect on caregiver ratings of behavioral regulation (b = .347, t [38] = 2.173, p = .036). However, family functioning did not have a significant independent effect on caregiver ratings of behavioral regulation (b = .181, t [38] = 1.138, p = .262).

The interaction term (Group_FAD_GF_Centered) was added to the equation in the second step of the hierarchical regression. The addition of the interaction term did not lead to a statistically significant increase in R^2 (ΔR^2 = .012, F [1, 36] = .526, p = .473). Family functioning did not moderate the impact of group membership on caregiver ratings of behavioral regulation with outliers included in the analysis.

Table 25.

Caregiver Ratings of Behavioral Regulation (With Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.202*	.202*
Constant	45.797	1.750			
Group membership	5.690	2.618	.347*		
Family functioning	3.140	2.758	.181		
Step 2				.213	.012
Constant	46.417	1.958			
Group membership	5.283	2.694	.322		
Family functioning	7.488	6.604	.433		
Group X Family functioning	-5.281	7.278	-.265		

Note. N = 40; * p < .05, ** p < .01, *** p < .001

The analysis was conducted again with the outliers removed. Results are presented in Table 26. In step one, group membership and family functioning accounted for 31.1% of the variance in caregiver ratings of behavioral regulation (F [2, 35] = 7.892,

$p < .001$). By itself, group membership did not have a significant effect on caregiver ratings of behavioral regulation ($b = .278$, t [36] = 1.848, $p = .073$). However, family functioning did have a significant independent effect on caregiver ratings of behavioral regulation ($b = .393$, t [36] = 2.610, $p = .013$). In step two, the addition of the interaction term did not lead to a statistically significant increase in R^2 ($\Delta R^2 = .000$, F [1, 34] = .006, $p = .938$). Therefore, family functioning did not moderate the impact of group membership on caregiver ratings of behavioral regulation with or without outliers removed. Because the interaction term was not statistically significant the follow-up analysis testing the regression coefficients separately by group was not conducted.

Table 26.

Caregiver Ratings of Behavioral Regulation (Without Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.311***	.311***
Constant	46.366	1.429			
Group membership	3.960	2.143	.278		
Family functioning	7.127	2.731	.393*		
Step 2				.311	.000
Constant	46.417	1.591			
Group membership	3.927	2.214	.276		
Family functioning	7.488	5.366	.413		
Group X Family functioning	-.492	6.265	-.022		

Note. $N = 38$; * $p < .05$, ** $p < .01$, *** $p < .001$

Hypothesis 2f.

Family functioning was expected to moderate the impact of group membership (survivor vs. healthy control) on scores on caregiver ratings of another aspect of executive functioning (metacognition). Furthermore, family functioning was expected to explain a significant amount of variance in scores on caregiver ratings of metacognition, above and beyond that accounted for by demographic and treatment-related variables in

the ALL group. In the control group, family functioning was not expected to account for a significant amount of additional variance in scores on caregiver ratings of metacognition beyond that accounted for by demographic variables.

In order to test for an interaction between group and family functioning on caregiver ratings of metacognition, a hierarchical regression analysis was performed. Results are presented in Table 27. Caregiver ratings of metacognition (the Metacognition Index score on the Parent Form of the BRIEF) was regressed on Group (survivor or healthy control) and family functioning (FAD_GF_Centered) using simultaneous multiple regression. These two variables accounted for 38.2% of the variance in caregiver ratings of metacognition on the Metacognition Index (F [2, 37] = 11.412, $p < .001$). By itself, group membership did not have a significant effect on caregiver ratings of metacognition ($b = .255$, t [38] = 1.815, $p = .078$). However, family functioning did have a significant independent effect on caregiver ratings of metacognition ($b = .472$, t [38] = 3.365, $p = .002$).

Table 27.

Caregiver Ratings of Metacognition (With Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.382***	.382***
Constant	49.044	2.043			
Group membership	5.548	3.057	.255		
Family functioning	10.837	3.221	.472**		
Step 2				.386	.004
Constant	48.533	2.294			
Group membership	5.885	3.157	.270		
Family functioning	7.249	7.738	.316		
Group X Family functioning	4.358	8.529	.165		

Note. $N = 40$; * $p < .05$, ** $p < .01$, *** $p < .001$

The interaction term (Group_FAD_GF_Centered) was added to the equation in the second step of the hierarchical regression. The addition of the interaction term did not lead to a statistically significant increase in R^2 (ΔR^2 = .004, F [1, 36] = .261, p = .612). Thus, this regression analysis indicated that family functioning did not moderate the impact of group membership on caregiver ratings of metacognition with outliers included in the analysis.

The analysis was conducted again with the outliers removed. Results are presented in Table 28. In step one, group membership and family functioning accounted for 32.3% of the variance in caregiver ratings of metacognition (F [2, 35] = 8.330, p = .001). By itself, group membership did not have a significant effect on caregiver ratings of metacognition (b = .224, t [36] = 1.499, p = .143). However, family functioning did have a significant independent effect on caregiver ratings of metacognition (b = .447, t [36] = 2.997, p = .005). In step two, the addition of the interaction term did not lead to a statistically significant increase in R^2 (ΔR^2 = .008, F [1, 34] = .406, p = .528). Therefore, this regression analysis indicated that family functioning did not moderate the impact of group membership on caregiver ratings of metacognition with or without outliers

Table 28.

Caregiver Ratings of Metacognition (Without Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.323***	.323***
Constant	49.103	1.964			
Group membership	4.417	2.946	.224		
Family functioning	11.251	3.754	.447**		
Step 2				.330	.008
Constant	48.533	2.174			
Group membership	4.782	3.026	.242		
Family functioning	7.249	7.335	.288		
Group X Family functioning	5.455	8.564	.177		

Note. N = 38; * p < .05, ** p < .01, *** p < .001

removed. Because the interaction term was not statistically significant the follow-up analysis testing the regression coefficients separately by group was not conducted.

Summary of results of main analyses.

A summary of the results of the main analyses is presented in Table 29. Tests for interaction effects revealed that the magnitude of the effect of group membership (survivor vs. healthy control) on multiple measures of neurocognitive functioning does not vary as a function of family functioning, with or without outliers included. Therefore, family functioning did not moderate the impact of group membership on performance on any of the measures of neurocognitive functioning. When outliers were included in the analysis, family functioning had significant independent effects on caregiver ratings of attention and on caregiver ratings of metacognition. With outliers included, group membership had significant independent effects on sustained attention, switching attention, cognitive flexibility (working memory), information processing (processing speed), and caregiver ratings of behavioral regulation. When outliers were removed from analyses, family functioning had significant independent effects on caregiver ratings of attention, caregiver ratings of behavioral regulation, and caregiver ratings of metacognition. Group membership had significant independent effects on divided attention, sustained attention, switching attention, and information processing (processing speed) with outliers removed.

Supplementary Analyses

As a follow up of the significant independent effects that were found, supplementary analyses were conducted. To investigate whether family functioning explains a significant amount of variance in scores on measures of neurocognitive functioning above and beyond that accounted for by demographic variables in the sample as a whole

and demographic and treatment-related variables in the ALL group, hierarchical multiple regression analyses were performed. Using a sequential regression, the control variables were entered first. For the sample as a whole, this included gender and SES. For the ALL group alone, this included gender, SES, age at diagnosis, and time since diagnosis. These were followed by family functioning as a predictor variable for the neurocognitive outcome measures.

With outliers included, the domains of neurocognitive functioning that were examined were caregiver ratings of attention and caregiver ratings of metacognition, as these were the domains in which there were significant independent effects for family functioning. Likewise, with outliers excluded, the domains of neurocognitive functioning that were examined were caregiver ratings of attention, caregiver ratings of behavioral regulation, and caregiver ratings of metacognition, as these were the domains in which there were significant independent effects for family functioning. The *p*-value associated with the change in R^2 was examined to determine if family functioning explains a significant amount of variance in neurocognitive outcome, even after controlling for demographic or demographic and treatment-related variables. A change in R^2 associated with an alpha of less than .05 was considered significant.

To further investigate the significant independent effects for group membership that were found, independent samples *t*-tests were performed to see if the two groups differed significantly in neurocognitive functioning. With outliers included, the domains of neurocognitive functioning investigated were sustained attention, switching attention, cognitive flexibility (working memory), information processing (processing speed), and caregiver ratings of behavioral regulation, as these were the domains in which there were significant effects for group membership. With outliers excluded, the domains investigated were divided attention, sustained attention, switching attention, and

Table 29.

Significant Results of Main Analyses of Outcome Measures

Analysis	With Outliers	Without Outliers
Hypothesis 1a: Selective Attention	Neither	Neither
Hypothesis 1b: Divided Attention	Neither	Group Membership
Hypothesis 1c: Sustained Attention	Group Membership	Group Membership
Hypothesis 1d: Switching Attention	Group Membership	Group Membership
Hypothesis 1e: Caregiver Ratings of Attention	Family Functioning	Family Functioning
Hypothesis 2a: Cognitive Flexibility (Working Memory)	Group Membership	Neither
Hypothesis 2b: Goal Setting (Planning)	Neither	Neither
Hypothesis 2c: Attentional Control (Inhibition)	Neither	Neither
Hypothesis 2d: Information Processing (Processing Speed)	Group Membership	Group Membership
Hypothesis 2e: Caregiver Ratings of Behavioral Regulation	Group Membership	Family Functioning
Hypothesis 2f: Caregiver Ratings of Metacognition	Family Functioning	Family Functioning

Note: Group Membership and Family Functioning were used as predictors in all analyses

information processing (processing speed), as these were the domains in which there were significant effects for group membership.

Family functioning with outliers included.

Caregiver ratings of attention.

In order to determine whether family functioning accounts for a significant amount of variance in caregiver ratings of attention above and beyond demographic variables in the sample as a whole with outliers included, a hierarchical multiple regression analysis was performed. Results are presented in Table 30. Gender and SES were entered in step 1. These two variables accounted for 14.5% of the variance in caregiver ratings of attention (F [2, 37] = 3.129, p = .056). Neither gender (b = -.293, t [38] = -1.926, p = .062) nor SES (b = .226, t [38] = 1.486, p = .146) by themselves had a significant effect on caregiver ratings of attention. In step 2, family functioning was entered. The addition of family functioning led to a statistically significant increase in R^2 (ΔR^2 = .299, F [1, 36] = 19.333, p < .001).

Table 30.

Caregiver Ratings of Attention in the Whole Sample (With Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.145	.145
Constant	49.579	3.359			
Gender	-5.895	3.061	-.293		
SES	5.094	3.428	.226		
Step 2				.444***	.299***
Constant	49.601	2.746			
Gender	-3.560	2.559	-.177		
SES	2.753	2.853	.122		
Family functioning	12.065	2.744	.570***		

Note. N = 40; * p < .05, ** p < .01, *** p < .001

In order to determine whether family functioning accounts for a significant amount of variance in caregiver ratings of attention above and beyond demographic and treatment variables in the clinical group with outliers included, a hierarchical multiple regression analysis was performed. Results are presented in Table 31. Gender, SES, age at diagnosis, and time since treatment were entered in step 2. These four variables accounted for 50.0% of the variance in caregiver ratings of attention (F [4, 15] = 3.745, p = .026). By itself, SES had a significant effect on caregiver ratings of attention (b = .448, t [18] = 2.408, p = .029). By themselves, gender (b = -.381, t [18] = -2.001, p = .064), age at diagnosis (b = .253, t [18] = 1.211, p = .245), and time since treatment (b = .376, t [18] = 1.841, p = .085) did not have significant independent effects on caregiver ratings of attention. In the second step, family functioning was added. The addition of family functioning did not lead to a statistically significant increase in R^2 (ΔR^2 = .113, F [1, 14] = 4.062, p = .063).

Table 31.

Caregiver Ratings of Attention in the Clinical Group (With Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.500*	.500*
Constant	37.051	8.202			
Gender	-7.958	3.978	-.381		
SES	9.608	3.990	.448*		
Age at Diagnosis	1.091	.900	.253		
Time Since Treatment	1.885	1.024	.376		
Step 2				.612	.113
Constant	40.438	7.661			
Gender	-5.5608	3.808	-.269		
SES	5.813	4.095	.271		
Age at Diagnosis	.893	.826	.207		
Time Since Treatment	1.365	.968	.272		
Family functioning	7.556	3.749	.414		

Note. N = 20; * p < .05, ** p < .01, *** p < .001

Results of these supplemental analyses indicate that family functioning accounts for a significant amount of variance in caregiver ratings of attention above and beyond demographic variables in the sample as a whole with outliers included. Within the clinical group alone, family functioning did not account for a significant amount of variance in caregiver ratings of attention above and beyond that accounted for by demographic and treatment variables when outliers were included. Rather, SES was the best predictor of caregiver ratings of attention within the clinical group with outliers included.

Caregiver ratings of metacognition.

In order to determine whether family functioning accounts for a significant amount of variance in caregiver ratings of metacognition above and beyond demographic variables in the sample as a whole with outliers included, a hierarchical multiple regression analysis was performed. Results are presented in Table 32. Gender and SES were entered in step 1. These two variables accounted for 11.3% of the variance in

Table 32.

Caregiver Ratings of Metacognition in the Whole Sample (With Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.113	.113
Constant	51.660	3.706			
Gender	-5.711	3.378	-.262		
SES	4.786	3.782	.196		
Step 2				.360**	.247**
Constant	51.682	3.191			
Gender	-3.409	2.973	-.157		
SES	2.479	3.315	.102		
Family functioning	11.890	3.188	.518**		

Note. $N = 40$; * $p < .05$, ** $p < .01$, *** $p < .001$

caregiver ratings of metacognition (F [2, 37] = 2.357, p = .109). Neither gender (b = -.262, t [38] = -1.691, p = .099) nor SES (b = .196, t [38] = 1.265, p = .214) by themselves had a significant effect on caregiver ratings of metacognition. In step 2, family functioning was entered. The addition of family functioning led to a statistically significant increase in R^2 (ΔR^2 = .247, F [1, 36] = 13.911, p = .001).

In order to determine whether family functioning accounts for a significant amount of variance in caregiver ratings of metacognition above and beyond demographic and treatment variables in the clinical group with outliers included, a hierarchical multiple regression analysis was performed. Results are presented in Table 33. Gender, SES, age at diagnosis, and time since treatment were entered in step 2. These four variables accounted for 63.6% of the variance in caregiver ratings of metacognition (F [4, 15] = 6.552, p = .003). By themselves, gender (b = -.429, t [18] = -2.641, p = .019), SES

Table 33.

Caregiver Ratings of Metacognition in the Clinical Group (With Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.636**	.636**
Constant	35.274	7.327			
Gender	-9.385	3.554	-.429*		
SES	9.405	3.565	.419*		
Age at Diagnosis	1.226	.804	.272		
Time Since Treatment	2.702	.914	.514*		
Step 2				.674	.038
Gender	37.338	7.356			
SES	-7.952	3.656	-.364*		
Age at Diagnosis	7.092	3.932	.316		
Time Since Treatment	1.106	.793	.245		
Gender	2.385	.929	.454*		
Family functioning	4.604	3.599	.241		

Note. N = 20; * p < .05, ** p < .01, *** p < .001

(b = .419, t [18] = 2.639, p = .019), and time since treatment (b = .514, t [18] = 2.955, p = .010) had a significant effect on caregiver ratings of metacognition. By itself, age at diagnosis did not have a significant independent effect on caregiver ratings of metacognition (b = .272, t [18] = 1.525, p = .148). In the second step, family functioning was added. The addition of family functioning did not lead to a statistically significant increase in R^2 (ΔR^2 = .038, F [1, 14] = 1.636, p = .222).

Results of these supplementary analyses indicate that family functioning accounts for a significant amount of variance in caregiver ratings of executive functioning (metacognition), above and beyond demographic variables, in the sample as a whole when outliers are included. Within the clinical group alone, family functioning did not account for a significant amount of variance in caregiver ratings of executive functioning (metacognition) above and beyond that accounted for by demographic and treatment variables with outliers included. Rather, gender, SES, and time since treatment were the best predictors of caregiver ratings of executive functioning (metacognition) within the clinical group when outliers were included.

Family functioning without outliers included.

Caregiver ratings of attention.

In order to determine whether family functioning accounts for a significant amount of variance in caregiver ratings of attention above and beyond demographic variables in the sample as a whole with outliers removed (N = 38), a hierarchical multiple regression analysis was performed. Results are presented in Table 34. Gender and SES were entered in step 1. These two variables accounted for 9.1% of the variance in caregiver ratings of attention (F [2, 35] = 1.749, p = .189). Neither gender (b = -.224, t [36] = -1.391, p = .173) nor SES (b = .196, t [36] = 1.215, p = .232) by themselves had a

significant effect on caregiver ratings of attention. In step 2, family functioning was entered. The addition of family functioning led to a statistically significant increase in R^2 ($\Delta R^2 = .391$, F [1, 34] = 16.754, $p < .001$).

Table 34.

Caregiver Ratings of Attention in the Whole Sample (Without Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.091	.091
Constant	48.574	3.135			
Gender	-4.052	2.913	-.224		
SES	3.898	3.207	.196		
Step 2				.391***	.300***
Constant	49.216	2.608			
Gender	-2.690	2.442	-.149		
SES	2.130	2.698	.107		
Family Functioning	12.902	3.152	.560***		

Note. $N = 38$; * $p < .05$, ** $p < .01$, *** $p < .001$

In order to determine whether family functioning accounts for a significant amount of variance in caregiver ratings of attention above and beyond demographic and treatment variables in the clinical group with outliers removed (n = 18), a hierarchical multiple regression analysis was performed. Results are presented in Table 35. Gender, SES, age at diagnosis, and time since treatment were entered in step 2. These four variables accounted for 37.5% of the variance in caregiver ratings of attention (F [4, 13] = 1.951, p = .162). By themselves, gender (b = -.370, t [16] = -1.626, p = .128), SES (b = .467, t [16] = 2.120, p = .054), age at diagnosis (b = .279, t [16] = 1.131, p = .278), and time since treatment (b = .255, t [16] = 1.066, p = .306) did not have a significant effect on caregiver ratings of attention. In the second step, family functioning was added. The addition of family functioning led to a statistically significant increase in R2 (ΔR2 = .251, F [1, 12] = 8.028, p = .015). This is a large effect according to Cohen (1988).

Table 35.

Caregiver Ratings of Attention in the Clinical Sample (Without Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.375	.375
Constant	39.389	8.990			
Gender	-6.696	4.119	-.370		
SES	8.622	4.068	.467		
Age at Diagnosis	1.029	.910	.279		
Time Since Treatment	1.341	1.259	.255		
Step 2				.626*	.251*
Constant	38.958	7.244			
Gender	-3.950	3.457	-.218		
SES	3.145	3.805	.170		
Age at Diagnosis	.914	.734	.248		
Time Since Treatment	1.625	1.019	.308		
Family Functioning	11.857	4.185	.599*		

Note. $N = 18$; * $p < .05$, ** $p < .01$, *** $p < .001$

Results of these supplemental analyses indicate that family functioning accounted for a significant amount of variance in caregiver ratings of attention, above and beyond demographic variables, in the sample as a whole when outliers were removed. Within the clinical group alone, family functioning accounted for a significant amount of variance in caregiver ratings of attention above and beyond that accounted for by demographic and treatment variables when outliers were removed.

Caregiver ratings of behavioral regulation.

In order to determine whether family functioning accounts for a significant amount of variance in caregiver ratings of behavioral regulation above and beyond demographic variables in the sample as a whole with outliers removed, a hierarchical multiple regression analysis was performed. Results are presented in Table 36. Gender and SES were entered in step 1. These two variables accounted for 8.1% of the variance in caregiver ratings of behavioral regulation (F [2, 35] = 1.543, p = .228). Neither gender

(b = -.253, t [36] = -1.562, p = .127) nor SES (b = -.137, t [36] = -.843, p = .405) by themselves had a significant effect on parent ratings of behavioral regulation. In step 2, family functioning was entered. The addition of family functioning led to a statistically significant increase in R^2 (ΔR^2 = .323, F [1, 34] = 12.130, p = .001).

Table 36.

Caregiver Ratings of Behavioral Regulation in the Whole Sample (Without Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.081	.081
Constant	51.602	2.483			
Gender	-3.603	2.307	-.253		
SES	-2.141	2.540	-.137		
Step 2				.323**	.323**
Constant	52.056	2.167			
Gender	-2.640	2.029	-.185		
SES	-3.390	2.242	-.216		
Family Functioning	9.122	2.619	.503**		

Note. N = 38; * p < .05, ** p < .01, *** p < .001

In order to determine whether family functioning accounts for a significant amount of variance in caregiver ratings of behavioral regulation above and beyond demographic and treatment variables in the clinical group with outliers removed, a hierarchical multiple regression analysis was performed. Results are presented in Table 37. Gender, SES, age at diagnosis, and time since treatment were entered in step 2. These four variables accounted for 11.5% of the variance in caregiver ratings of behavioral regulation (F [4, 13] = .424, p = .789). By themselves, gender (b = -.219, t [16] = -.808, p = .434), SES (b = .147, t [16] = .559, p = .586), age at diagnosis (b = -.043, t [16] = -.147, p = .885), and time since treatment (b = .179, t [16] = .629, p = .541) did not have a significant effect on caregiver ratings of behavioral regulation. In the second step, family

functioning was added. The addition of family functioning did not lead to a statistically significant increase in R^2 (ΔR^2 = .184, F [1, 36] = 3.156, p = .101).

Table 37.

Caregiver Ratings of Behavioral Regulation in the Clinical Sample (Without Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.115	.115
Constant	48.439	8.131			
Gender	-3.011	3.725	-.219		
SES	2.057	3.679	.147		
Age at Diagnosis	-.121	.823	-.043		
Time Since Treatment	.716	1.139	.179		
Step 2				.300	.184
Constant	48.158	7.532			
Gender	-1.220	3.594	-.089		
SES	-1.514	3.956	-.108		
Age at Diagnosis	-.196	.763	-.070		
Time Since Treatment	.900	1.060	.225		
Family Functioning	7.730	4.351	.514		

Note. N = 18; * p < .05, ** p < .01, *** p < .001

Results of these supplementary analyses indicate that family functioning accounted for a significant amount of variance in caregiver ratings of executive functioning (behavioral regulation), above and beyond demographic variables, in the sample as a whole when outliers were removed. Within the clinical group alone, family functioning did not account for a significant amount of variance in caregiver ratings of executive functioning (behavioral regulation) above and beyond that accounted for by demographic and treatment variables when outliers were removed.

Caregiver ratings of metacognition.

In order to determine whether family functioning accounts for a significant amount of variance in caregiver ratings of metacognition above and beyond demographic variables in the sample as a whole with outliers removed, a hierarchical multiple

regression analysis was performed. Results are presented in Table 38. Gender and SES were entered in step 1. These two variables accounted for 6.3% of the variance in caregiver ratings of metacognition (F [2, 35] = 1.181, p = .319). Neither gender (b = -.189, t [36] = -1.156, p = .256) nor SES (b = .161, t [36] = .985, p = .332) by themselves had a significant effect on caregiver ratings of metacognition. In step 2, family functioning was entered. The addition of family functioning led to a statistically significant increase in R^2 (ΔR^2 = .300, F [1, 34] = 11.515, p = .002).

Table 38.

Caregiver Ratings of Metacognition in the Whole Sample (Without Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.063	.063
Constant	50.582	3.477			
Gender	-3.733	3.230	-.189		
SES	3.502	3.557	.161		
Step 2				.300**	.237**
Constant	51.205	3.054			
Gender	-2.410	2.860	-.122		
SES	1.786	3.160	.082		
Family Functioning	12.527	3.692	.498**		

Note. N = 38; * p < .05, ** p < .01, *** p < .001

In order to determine whether family functioning accounts for a significant amount of variance in caregiver ratings of metacognition above and beyond demographic and treatment variables in the clinical group with outliers removed, a hierarchical multiple regression analysis was performed. Results are presented in Table 39. Gender, SES, age at diagnosis, and time since treatment were entered in step 2. These four variables accounted for 55.4% of the variance in caregiver ratings of metacognition (F [4, 13] = 4.039, p = .024). By themselves, gender (b = -.460, t [16] = -2.392, p = .033), SES (b = .454, t [16] = 2.439, p = .030), and time since treatment (b = .487, t [16] = 2.416, p =

.031) had a significant effect on caregiver ratings of metacognition. By itself, age at diagnosis did not have a significant independent effect on caregiver ratings of metacognition (b = .324, t [16] = 1.554, p = .144). In the second step, family functioning was added. The addition of family functioning led to a statistically significant increase in R^2 (ΔR^2 = .160, F [1, 12] = 6.718, p = .024). This is a medium to large effect according to Cohen (1988).

Table 39.

Caregiver Ratings of Metacognition in the Clinical Sample (Without Outliers)

	B	*SE B*	β	R^2	ΔR^2
Step 1				.554*	.554*
Constant	34.894	7.972			
Gender	-8.738	3.652	-.460*		
SES	8.798	3.607	.454*		
Age at Diagnosis	1.254	.807	.324		
Time Since Treatment	2.697	1.116	.487*		
Step 2				.714*	.160*
Constant	34.532	6.645			
Gender	-6.433	3.171	-.338		
SES	4.202	3.490	.217		
Age at Diagnosis	1.157	.673	.299		
Time Since Treatment	2.935	.935	.530**		
Family Functioning	9.949	3.838	.479*		

Note. N = 18; * p < .05, ** p < .01, *** p < .001

Results of these supplemental analyses indicate that family functioning accounted for a significant amount of variance in caregiver ratings of executive functioning (metacognition), above and beyond demographic variables, in the sample as a whole when outliers were removed. Within the clinical group alone, family functioning accounted for a significant amount of variance in caregiver ratings of executive functioning (metacognition) above and beyond that accounted for by demographic and treatment variables when outliers were removed.

Summary of family functioning supplemental analyses.

A summary of the family functioning supplemental analyses is presented in Table 40. As a follow-up of the significant independent effects for family functioning that were found in the original analyses, supplementary analyses were conducted. For the sample as a whole, with outliers included, family functioning explained a significant amount of variance in scores on measures of caregiver ratings of attention and executive functioning (metacognition), above and beyond that accounted for by demographic variables (gender and SES). Without outliers included, family functioning explained a significant amount of variance in scores on measures of caregiver ratings of attention and executive functioning (behavioral regulation and metacognition), above and beyond that accounted for by demographic variables in the sample as a whole.

For the clinical group alone, with outliers included, family functioning did not explain a significant amount of variance in scores on measures of caregiver ratings of attention and executive functioning (metacognition), above and beyond that accounted for by demographic variables and treatment variables (age at diagnosis and time since treatment). Without outliers included, for the clinical group alone, family functioning explained a significant amount of variance in scores on measures of caregiver ratings of attention and metacognition, above and beyond that accounted for by demographic variables and treatment variables, but did not explain a significant amount of variance in scores on measures of caregiver ratings of behavioral regulation above and beyond that accounted for by demographic and treatment variables.

Table 40.

Summary of Family Functioning Supplemental Analyses

Analysis	With Outliers		Without Outliers	
	Whole Sample	Clinical Group	Whole Sample	Clinical Group
Caregiver Ratings of Attention	Significant	Not significant	Significant	Significant
Caregiver Ratings of Behavioral Regulation	-	-	Significant	Not significant
Caregiver Ratings of Metacognition	Significant	Not significant	Significant	Significant

Note: With the sample as a whole, there were two demographic variables (gender and SES) entered before family functioning. With the clinical group alone, there were two demographic variables (gender and SES) and two treatment-related variables (age at diagnosis and time since treatment) entered before family functioning.

Group membership supplemental analyses.

Assumptions of t-tests.

Given that group membership had a significant independent effect on several of the neurocognitive outcome measures, independent samples *t*-tests were used to test the significance of apparent group differences in the relevant neurocognitive domains. This was done in order to determine if the two groups' scores were significantly different without controlling for family functioning. Prior to analysis, the assumptions for *t*-tests were examined. Normal sampling distribution was examined using the Kolmogorov-Smirnov test. With outliers included, cognitive flexibility (working memory; D [20] = .240, p = .004) and sustained attention (D [20] = .216, p = .015) were significantly non-normal. With outliers removed, cognitive flexibility (working memory) in the clinical group (D [18] = .203, p = .048) and divided attention in the control (D [20] = .217, p = .015) and clinical (D [18] = .205, p = .045) groups were significantly non-normal. All other variables of interest were normally distributed in the sample.

Homogeneity of variance was examined using Levine's test. With outliers included, the variances were equal for the two groups for sustained attention (F [1, 39] = .412, p = .525), switching attention (F [1,39] = 2.371, p = .132), cognitive flexibility (working memory; F [1, 39] = 1.984, p = .167), information processing (processing speed; F [1, 39] = 3.470, p = .070), and caregiver ratings of behavioral regulation (F [1, 39] = 1.089, p = .303). With outliers removed, variances were equal for the two groups for divided attention (F [1, 36] = 2.876, p = .099), sustained attention (F [1, 36] = .691, p = .411), switching attention (F [1, 36] = 4.051, p = .052), and cognitive flexibility (working memory; F [1, 36] = 2.815, p = .102). For information processing (processing

speed) the variances were significantly different in the two groups, (F [1, 36] = 4.266, p = .046).

With outliers included.

With outliers included, the neurocognitive domains examined were sustained attention, switching attention, cognitive flexibility (working memory), information processing (processing speed), and caregiver ratings of behavioral regulation. Results are presented in Table 41. Participants in the control group performed statistically significantly better than participants in the clinical group on tests of sustained attention, t (38) = 2.222, p = .032; switching attention, t (38) = 2.644, p = .012; cognitive flexibility (working memory), t (38) = 2.518, p = .016; information processing (processing speed), t (38) = 2.894, p = .006; and caregiver ratings of behavioral regulation, t (38) = -2.829, p = .007.

Table 41.

Group Differences (With Outliers)

	M	*SD*	*t*	*df*	*p*
Sustained Attention			2.222	38	.032
Control	10.25	3.007			
Clinical	8.00	3.387			
Switching Attention			2.644	38	.012
Control	10.55	2.328			
Clinical	8.20	3.222			
Cognitive Flexibility (Working Memory)			2.518	38	.016
Control	103.90	10.622			
Clinical	93.45	15.219			
Information Processing (Processing Speed)			2.894	38	.006
Control	104.20	10.768			
Clinical	91.75	15.940			
Caregiver Ratings of Behavioral Regulation			-2.829	38	.007
Control	45.35	6.235			
Clinical	52.20	8.853			

With outliers removed.

With outliers excluded, the domains investigated were divided attention, sustained attention, switching attention, cognitive flexibility (working memory), and information processing (processing speed). Results are presented in Table 42. Participants in the control group performed statistically significantly better than participants in the clinical group on tests of switching attention, t (36) = 2.429, p = .020; cognitive flexibility (working memory), t (36) = 2.259, p = .030; and information processing (processing speed), t (28.949) = 2.565, p = .016. Participants in the control group also performed better than participants in the clinical group on tests of sustained attention, t (36) = 1.924, p = .062, and divided attention, t (36) = 1.664, p = .105, but these differences were not statistically significant.

Table 42.

Group Differences (Without Outliers)

	M	*SD*	*t*	*df*	*p*
Divided Attention			1.664	36	.105
Control	8.20	3.778			
Clinical	6.06	4.165			
Sustained Attention			1.924	36	.062
Control	10.25	3.007			
Clinical	8.22	3.490			
Switching Attention			2.429	36	.020
Control	10.55	2.328			
Clinical	8.28	3.392			
Cognitive Flexibility (Working Memory)			2.259	36	.030
Control	103.90	10.622			
Clinical	94.06	15.969			
Information Processing (Processing Speed)			2.565	28.949	.016
Control	104.20	10.768			
Clinical	92.56	16.325			

Summary of group membership supplemental analyses.

A summary of the group membership supplemental analyses is presented in Table 43. As a follow up of the significant independent effects for group membership that were found in the original analyses, supplementary analyses were conducted. With outliers included, the control group performed significantly better than the clinical group on measures of sustained attention, switching attention, cognitive flexibility (working memory), information processing (processing speed), and caregiver ratings of behavioral regulation. Without outliers included, the control group performed significantly better than the clinical group on measures of switching attention, cognitive flexibility (working memory), and information processing (processing speed). The control group also performed better than the clinical group on measures of divided attention and sustained attention, but the difference was not statistically significant.

Table 43.

Summary of Group Membership Supplemental Analyses

Analysis	With Outliers	Without Outliers
Hypothesis 1a: Selective Attention	Not included	Not included
Hypothesis 1b: Divided Attention	Not included	Control > Clinical
Hypothesis 1c: Sustained Attention	Control > Clinical*	Control > Clinical
Hypothesis 1d: Switching Attention	Control > Clinical*	Control > Clinical*
Hypothesis 1e: Caregiver Ratings of Attention	Not included	Not included
Hypothesis 2a: Cognitive Flexibility (Working Memory)	Control > Clinical*	Control > Clinical*
Hypothesis 2b: Goal Setting (Planning)	Not included	Not included
Hypothesis 2c: Attentional Control (Inhibition)	Not included	Not included
Hypothesis 2d: Information Processing (Processing Speed)	Control > Clinical**	Control > Clinical*
Hypothesis 2e: Caregiver Ratings of Behavioral Regulation	Control > Clinical**	Not included
Hypothesis 2f: Caregiver Ratings of Metacognition	Not included	Not included

Note: * $p < .05$, ** $p < .01$, *** $p < .001$

Chapter 5: Discussion

This study investigated the effect of family functioning upon neurocognitive outcome among survivors of pediatric ALL treated with chemotherapy, specifically in the domains of attention and executive functioning, compared with a group of healthy control children. It was expected that for the ALL group, but not for the comparison group, family functioning would explain a significant amount of variance in neurocognitive outcome, even after controlling for demographic and treatment-related variables. These hypotheses were generated based on previous research among pediatric traumatic brain injury and pediatric brain tumor populations that found that positive family functioning serves as a protective factor for neurocognitive outcomes of children who survive these conditions.

Summary of Results

The investigator had two primary research questions: (1) Does positive family functioning protect against deficits in attention among survivors of pediatric ALL, specifically in the subdomains of selective attention, divided attention, sustained attention, and shifting attention, and as reported by caregivers? (2) Does positive family functioning protect against deficits in executive functioning among survivors of pediatric ALL, specifically in the subdomains (areas) of cognitive flexibility (working memory), goal setting (planning), attentional control (inhibition), information processing (processing speed) and as reported by caregivers (behavioral regulation and metacognition)? It was hypothesized that family functioning would be associated with these domains of neurocognitive functioning among survivors of pediatric ALL but not among healthy control children. Contrary to expectations, the relationship between family functioning and neurocognitive functioning did not differ by group (survivor vs. healthy

control) for any of the domains listed above. That is, the negative effects of cancer treatment upon neurocognitive functioning were not any more severe among children from families with greater levels of family dysfunction than those children from families with better family functioning.

Supplemental analyses indicated that, across the sample as whole (survivors and healthy controls), family functioning was associated with caregiver ratings of attention and metacognition. Without outliers included, it was also associated with caregiver ratings of behavioral regulation. That is, children (both survivors and healthy control children) whose caregivers endorsed higher levels of family dysfunction (difficulty engaging in the interactional patterns necessary for the achievement of family goals) also rated their children as having more difficulty maintaining necessary levels of attention; shifting their cognitive set and modulating their emotions and behavior via appropriate inhibitory control; and initiating, planning, organizing, self-monitoring, and sustaining working memory.

Family functioning was not found to be associated with performance-based measures of attention or executive functioning for survivors or healthy control participants. That is, for the sample as a whole, family functioning was not associated with performance on measures of selective attention, divided attention, sustained attention, shifting attention, cognitive flexibility/working memory, goal setting/planning, attentional control/inhibition, or information processing/processing speed. Children from families with higher levels of family dysfunction did not perform any worse in these domains than children from families with better family functioning.

Supplemental analyses also revealed that group membership (survivor vs. healthy control) was associated with neurocognitive functioning in the domains of sustained attention, switching attention, cognitive flexibility/working memory, information

processing/processing speed, divided attention (without outliers only), and caregiver rated behavioral regulation (with outliers only) domains. That is, children in the healthy control group performed significantly better than children in the survivor group on tests of switching attention, cognitive flexibility/working memory, and information processing/processing speed. With outliers included, the control group also performed significantly better than the clinical group on measures of sustained attention and caregiver rated behavioral regulation.

No Interaction Effects

Contrary to what was expected, family functioning did not have a differential effect on neurocognitive functioning for survivors of pediatric ALL as compared to healthy children. It had been hypothesized, based on previous literature in the pediatric TBI population that compared children who survived a TBI with children who survived an orthopedic injury, that such a differential effect would be found (Max et al., 1999; Nadebaum et al., 2007; Taylor et al., 1999; Yeates et al., 1997). It is thought that perhaps the neurological impairment suffered by children who sustain a TBI makes them more vulnerable to family influence than their peers who have not sustained such neurological damage (Taylor et al., 1999). Likewise, it was hypothesized that pediatric ALL survivors would be more vulnerable to the effects of family functioning upon neurocognitive functioning than children who had not experienced cancer treatment. The current study was the first known study to investigate the relationship between family functioning and neurocognitive functioning among the ALL population.

A potential explanation for the lack of a differential effect of family functioning upon neurocognitive functioning among survivors of ALL treated with chemotherapy alone as compared to healthy children may be that this subset of ALL survivors do not

suffer sufficient neurological impairment from their treatment to make them more vulnerable to family influence than their peers who have not received cancer treatment. Indeed, current treatment protocols that utilize chemotherapy alone were developed in large part to reduce the neurotoxic effects of previous treatment protocols that utilized CRT (van der Plas et al., 2015). Although research has found significant differences on neuroimaging, particularly in white matter, among survivors of ALL treated with chemotherapy alone as compared with healthy children, these differences are more subtle than the neurological deficits found among survivors of pediatric TBI or BT (Kunin-Batson et al., 2014; van der Plas et al., 2015). Survivors of pediatric ALL treated with chemotherapy have been found to have lesions in deep white matter, reduced white matter volume, and alterations in white matter tract development (van der Plas et al., 2015). However, gray matter appears to be relatively spared in this population (van der Plas et al., 2015). Survivors of pediatric brain tumor also experience damage to white matter but to a greater extent than ALL survivors (i.e., greater white matter volume loss; Reddick et al., 2014). The neuropathology of TBI often includes damage to white matter and gray matter, increased cerebrospinal fluid volume, and decreased whole brain volume (Bigler et al., 2013). This damage may further progress over time (Yeates 2009). The more severe neurological impacts experienced by survivors of pediatric brain tumor and TBI, as compared to survivors of pediatric ALL, may be what make these populations more vulnerable to family functioning than the ALL population.

Another potential explanation is that children who suffer a TBI or undergo a brain tumor resection sometimes experience difficulties in functioning independently due to deficits in motor, self-care, or language skills (Giordana & Clara, 2006; Yeates, 2009). These difficulties make them more dependent upon their caregivers for completing activities of daily living (Taylor et al., 1999). Such functional impairments, which are

less prevalent among survivors of ALL treated with chemotherapy alone, and the dependence upon caregivers that they create, may contribute to making these populations more vulnerable to family influences than the ALL population.

Another possible explanation for the lack of a differential effect may be that the FAD GFS might not be sensitive to the particular issues faced by families of childhood ALL survivors. Some researchers in this field have suggested using measures of family functioning designed particularly for families of youth with chronic health conditions (Hocking et al., 2015). Perhaps using a measure that is more sensitive to the particular issues faced by families of childhood ALL survivors would have captured a differential effect of family functioning on neurocognitive functioning among survivors compared with healthy controls.

Alternatively, there are methodological differences in the current study that may have contributed to the lack of expected findings. For one, the sample size of the current study was smaller than most of the studies examining family functioning and neurocognitive functioning among pediatric TBI and pediatric brain tumor populations (Carlson-Green et al., 1995; Max et al., 1999; Nadebaum et al., 2007; Taylor et al., 1999; Yeates et al., 1997). It may be that the current study was under-powered to find a significant interaction effect between family functioning and group membership in accounting for differences in neurocognitive functioning.

The one former study with a similar sample size (24 participants in the severe TBI group, 24 in the moderate TBI group, and 24 in the OI group) utilized a "psychosocial disadvantage factor" comprised of family functioning and family psychiatric history in predicting difference in IQ and memory, as opposed to family functioning alone (Max et al., 1999). Similarly, in one of the studies examining family functioning among pediatric brain tumor survivors, family factors (specifically, maternal coping resources) as opposed

to family functioning per se were significantly associated with neurocognitive outcomes in survivors (Carlson-Green et al., 1995).

Some of the previous studies used different measures of family functioning than that used in the current study, which could also explain differences in results. Max et al. (1999) used the Mc-SIFF, a clinical research interview based on the MMFF, as opposed to a caregiver-report measure. Nadebaum et al. (2007) used the Family Functioning Questionnaire, which assesses three domains of family functioning (i.e., conflict, intimacy, and democratic parenting style). Carlson-Green and colleagues (1995) and Ach and colleagues (2013) used the Family Environment Scale, which assesses three domains of the social environment within the family (i.e., supportiveness, conflict, and control).

Caregiver Ratings vs. Performance-Based Measures of Attention and Executive Functioning

Although the expected interaction effects were not found, some significant independent effects for family functioning were found. Family functioning was significantly associated with caregiver ratings of attention and executive functioning for both survivors and healthy controls. That is, among the whole sample, caregivers who viewed their family as having difficulties with family functioning were more likely to view their child as having difficulties with attention and executive functioning. Family functioning was not significantly associated with performance-based measures of attention/executive functioning for either group (survivor or healthy control).

The fact that caregiver ratings of family functioning were significantly related to caregiver ratings of attention/executive functioning, but not to performance-based measures of attention/executive functioning, may reflect single source bias, as the same person (the caregiver) was rating the family's functioning and rating the child's attention/executive functioning (Hocking et al., 2015). This is consistent with literature

that has found that, among both community and clinical samples, parent ratings of family functioning are highly correlated with parent ratings of children's behavioral and emotional functioning (Kinsman, Wildman, & Smucker, 1999). It has been suggested that perhaps parent report of child or family problems serve as proxies for parent psychosocial distress.

Group Differences in Attention and Executive Functioning

As expected based upon the literature on neurocognitive late effects among survivors of pediatric ALL, children with a history of ALL performed worse than healthy peers on measures of sustained attention (Reddick et al., 2006), working memory (Ashford et al., 2010; Carey et al., 2008; Iyer et al., 2015; Kingma et al., 2002; Lesnik et al., 1998; Waber et al., 1995), and processing speed (Iyer et al., 2015; Jansen, 2008). Working memory and processing speed in particular have most consistently been found to be impaired within this population as compared to healthy controls.

On average, children in the survivorship group also performed worse than children in the healthy control group on the other domains of attention (selective, divided, switching) and executive functioning (planning, inhibition) assessed in this study, but these differences were not significant. It may be that the small sample size of the study limited the power to find significant group differences within these domains. However, there have been more mixed findings in the literature regarding whether or not these domains are affected in this population (Iyer et al., 2015).

Summary of Integration of Results

This study was the first known study to examine the relationship between family functioning and neurocognitive functioning among survivors of pediatric ALL treated with chemotherapy alone. Contrary to what has been found within the pediatric TBI and

pediatric brain tumor populations, results of this study indicate that family functioning does not moderate neurocognitive functioning among this population. That is, differences in neurocognitive functioning between survivors and healthy controls were no more pronounced among those from families reporting higher degrees of dysfunction than those from families reported more optimal family functioning.

For both groups of children in this study, survivors and healthy controls, those from families rated by caregivers as having higher degrees of family dysfunction were rated by their caregivers as having more difficulties with attention and executive functioning. This is not unexpected given that high rates of correlation have been found between caregiver ratings of family functioning and caregiver ratings of children's functioning in both clinical and non-clinical samples.

This study contributes to the literature on neurocognitive late effects among survivors of pediatric ALL treated with chemotherapy alone. Survivors in the current sample performed significantly worse than healthy peers on measures of sustained attention, working memory, and processing speed. Working memory and processing speed have been consistently found to be areas of relative weakness for this population. While attention overall has been one of the domains most commonly found to be affected among this population, there have been fewer studies looking at specific subdomains of attention, particularly sustained attention. Thus, this study helps increase our understanding of the specific subdomains of attention that may be most impacted among this population.

Limitations

There are several limitations that should be mentioned in this study. First of all, there was generally a lack of variability in family functioning, particularly if outliers were

removed. This may be due at least in part to a form of selection bias, in that perhaps the people who volunteer for research studies (particularly those about family functioning) are from families that have higher levels of functioning. It is possible that the restricted range of family functioning may have impacted the results of this study. Additionally, the families and patients who participated in this study may not be representative of the larger population of childhood ALL survivors and their families. Furthermore, the sample size in this study was small and there may not have been sufficient power to detect significant effects. Also, given that this study was cross sectional as opposed to longitudinal, it is not possible to determine directional or causal associations between the variables.

Another limitation of this study is the potential for single-rater bias, given that caregivers filled out rating forms of their child's attention and executive functioning as well as the family functioning measure. Additionally, there was only a single rating of family functioning for each participant. Best practice would have been to have multiple members of the family rate the family's functioning, and/or to include a clinician rating based on interview or observation of a family task. Similarly, there was only one rating of children's attention and executive functioning. Best practice would be to have more than one informant, such as obtaining a teacher or second caregiver perspective as well.

Recommendations for Future Research

The findings of this study and the aforementioned limitations suggest many possible directions for future research. First of all, obtaining a larger sample size would assist with ensuring there is sufficient power to detect possible interaction effects. Utilizing a longitudinal design, as opposed to cross sectional, would allow for examination of the directionality of the association between family functioning and

neurocognitive functioning. Furthermore, obtaining additional perspectives on participants' attention and executive functioning, such as through teacher ratings, could be of value.

Future studies could obtain a more robust assessment of family functioning by collecting ratings from multiple members of each family (i.e., multiple caregivers, child) or by utilizing clinician-rated measures of family functioning. In addition, future studies could examine specific aspects of family functioning (i.e., roles, behavior control, problem solving, etc.) as opposed to utilizing global measures of family functioning as was used in this study, to see if specific domains of family functioning are particularly associated with neurocognitive functioning. Alternatively, it might be worth utilizing a measure of family functioning that is more specific to families of children with chronic health conditions. Finally, utilizing a mixed-methods approach and including a qualitative component would allow for a richer understanding of family functioning among this population.

Implications for Clinical Practice

Although the current study is correlational in nature and thus no directionality can be inferred, results suggest a relationship between family dysfunction and difficulties with children's attention/executive functioning as reported by caregivers. As such, elevated caregiver ratings of a survivor's attention or executive functioning, particularly in the absence of low scores on performance-based measures of attention or executive functioning, could be a signal for the clinician to consider the caregiver's perception of the family's functioning and could suggest the need to assess for the need for additional supports for the caregiver and family. In such cases, family intervention may be warranted. Within the multidisciplinary clinic or hospital setting, social work could assist

with providing services to families identified as having difficulties with family functioning.

This study's findings that family functioning does not moderate neurocognitive functioning among survivors of ALL treated with chemotherapy could be good news for the families of these survivors. Very often, parents of childhood ALL survivors experience anxiety and guilt about whether anything they have done is contributing to their child's functioning. The results of this study could provide some relief to these families, letting them know that they are not to blame if their child is experiencing difficulties with attention or executive functioning.

Finally, this study found evidence for the existence of neurocognitive late effects among survivors of pediatric ALL treated with chemotherapy alone. As such, it provides support for the need for ongoing monitoring of neurocognitive functioning among this population. Furthermore, this study investigated specific subdomains of attention and executive functioning and found some to be more affected in this population than others. This suggests that it is important to assess these particular subdomains, as opposed to simply assessing for attention or executive functioning more globally, as knowledge of the specific subdomains affected may help target interventions and potentially make them more effective. Such information could be invaluable for teachers and others working with survivors experiencing difficulties with attention and executive functioning.

Conclusion

Contrary to expectations, family functioning did not have a differential association with neurocognitive functioning among survivors of pediatric ALL as compared with healthy control children. For survivors and healthy children, family functioning was significantly associated with caregiver ratings of children's attention and

executive functioning. Family functioning was not associated with performance-based measures of attention or executive functioning for survivors or healthy control children. This was the first known study to examine the relation between family functioning and neurocognitive functioning among survivors of pediatric ALL and the results suggest many avenues for future study.

Appendices

Appendix A: Consent Form

Consent for Participation in Research

Title: Family Functioning as a Moderator of Neurocognitive Outcome Among Survivors of Pediatric Acute Lymphoblastic Leukemia

Introduction

The purpose of this form is to provide you information that may affect your decision as to whether or not to participate in this research study. The person performing the research will answer any of your questions. Read the information below and ask any questions you might have before deciding whether or not to take part. If you decide to be involved in this study, this form will be used to record your consent.

Purpose of the Study

You have been asked to participate in a research study about the effect of family functioning upon neurocognitive outcome among survivors of pediatric ALL treated with chemotherapy. The purpose of this study is to determine if positive family functioning serves as a protective factor against the neurocognitive deficits commonly seen in this population.

What will you be asked to do?

If you agree to participate in this study, you will be asked to complete questionnaires about your child's emotional and behavioral functioning and your family's functioning.

Your child will be asked to participate in neuropsychological tasks to measure attention and executive functioning.

This study will take 90 minutes and will include approximately 60 study participants.

What are the risks involved in this study?

Minimal risk in participating in this study includes emotional distress from completing measures. If this occurs, emotional support will be provided by a licensed psychologist.

Another possible risk that all participants may incur by participating in this study is a loss of confidentiality if study measures were to be lost. This risk will be addressed by: (i) use of subject numbers only to label any study materials and (ii) storage of all completed measures in a designated locked cabinet separate from the roster that links subject numbers with names of participants.

Any incident that occurs that in any way compromises the rights or welfare of the participants will be reported by the principal investigator to the Institutional Review Board within five days of its occurrence as an unanticipated event, per board policy.

What are the possible benefits of this study?

You will receive no direct benefit from participating in this study; however, you may enjoy positive emotions associated with your contribution to informing the field of research in psychology as applied to medical populations.

Do you have to participate?

No, your participation is voluntary. You may decide not to participate at all or, if you start the study, you may withdraw at any time. Withdrawal or refusing to participate will not affect your relationship with The University of Texas at Austin in anyway.

If you would like to participate please sign below. You will receive a copy of this form.

Will there be any compensation?

Your child will receive a $5 gift certificate from Target as compensation for your participation in this study. Payments will occur after completion of neuropsychological tasks and questionnaires. You will be responsible for any taxes assessed on the compensation. If you or your child decide to withdraw from the study, your child will still receive the compensation.

How will your privacy and confidentiality be protected if you participate in this research study?

Your privacy and the confidentiality of your data will be protected by randomly assigning you a number (ranging from 001 to 100) at the outset of the study. All completed forms will be de-identified. A roster of individual names and their corresponding participant numbers will be maintained in a separate, locked filing cabinet from the participant forms. Your privacy will be protected by providing a private place for you to complete questionnaires and neuropsychological tasks.

If it becomes necessary for the Institutional Review Board to review the study records, information that can be linked to you will be protected to the extent permitted by law. Your research records will not be released without your consent unless required by law or a court order. The data resulting from your participation may be made available to other researchers in the future for research purposes not detailed within this consent form. In these cases, the data will contain no identifying information that could associate it with you, or with your participation in any study.

Participants will be given notice at least twenty-four hours prior to a researcher's arrival at their homes or other non-public places where they will be tested. Researchers will not show up unannounced. If the researcher(s) observe or otherwise learn of child or elder abuse while visiting your home, confidentiality will be broken: state law requires the reporting of abuse to relevant agencies. If I should observe or otherwise learn of child or elder abuse while visiting the participant's home, confidentiality will be broken. The researcher will report the abuse to relevant agencies (Child Protective Services or the Texas Department of Family and Protective Services) as required by law.

Whom to contact with questions about the study?

Prior, during or after your participation you can contact the researcher Thea Norris at (405) 742-4389 or send an email to thea.norris@utexas.edu for any questions or if you feel that you have been harmed.

This study has been reviewed and approved by The University Institutional Review Board and the study number is 2014-04-0112.

Whom to contact with questions concerning your rights as a research participant?

For questions about your rights or any dissatisfaction with any part of this study, you can contact, anonymously if you wish, the Institutional Review Board by phone at (512) 471-8871 or email at orsc@uts.cc.utexas.edu.

Participation

If you agree to participate please sign below.

Signature

You have been informed about this study's purpose, procedures, possible benefits and risks, and you have received a copy of this form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask other questions at any time. You voluntarily agree to participate in this study. By signing this form, you are not waiving any of your legal rights.

_____
Printed Name

_____ _____
Signature Date

As a representative of this study, I have explained the purpose, procedures, benefits, and the risks involved in this research study.

_____
Print Name of Person obtaining consent

_____ _____
Signature of Person obtaining consent Date

Appendix B: Permission Form

Parental Permission for Children Participation in Research

Title: Family Functioning as a Moderator of Neurocognitive Outcome Among Survivors of Pediatric Acute Lymphoblastic Leukemia

Introduction

The purpose of this form is to provide you (as the parent of a prospective research study participant) information that may affect your decision as to whether or not to let your child participate in this research study. The person performing the research will describe the study to you and answer all your questions. Read the information below and ask any questions you might have before deciding whether or not to give your permission for your child to take part. If you decide to let your child be involved in this study, this form will be used to record your permission.

Purpose of the Study

If you agree, your child will be asked to participate in a research study about the effect of family functioning upon neurocognitive outcome among survivors of pediatric ALL treated with chemotherapy. The purpose of this study is to determine if positive family functioning serves as a protective factor against the neurocognitive deficits commonly seen in this population.

What is my child going to be asked to do?

If you allow your child to participate in this study, they will be asked participate in neuropsychological tasks to measure attention and executive functioning. This study will take 90 minutes and will include approximately 60 study participants.

What are the risks involved in this study?

Minimal risk in participating in this study includes emotional distress from completing measures. If this occurs, emotional support will be provided by a licensed psychologist.

Another possible risk that all participants may incur by participating in this study is a loss of confidentiality if study measures were to be lost. This risk will be addressed by: (i) use of subject numbers only to label any study materials and (ii) storage of all completed measures in a designated locked cabinet separate from the roster that links subject numbers with names of participants.

Any incident that occurs that in any way compromises the rights or welfare of the participants will be reported by the principal investigator to the Institutional Review Board within five days of its occurrence as an unanticipated event, per board policy.

What are the possible benefits of this study?

Your child will receive no direct benefit from participating in this study; however, they may enjoy positive emotions associated with your contribution to informing the field of research in psychology as applied to medical populations.

Does my child have to participate?

No, your child's participation in this study is voluntary. Your child may decline to participate or to withdraw from participation at any time. Withdrawal or refusing to participate will not affect their relationship with The University of Texas at Austin in anyway. You can agree to allow your child to be in the study now and change your mind later without any penalty.

What if my child does not want to participate?

In addition to your permission, your child must agree to participate in the study. If you child does not want to participate they will not be included in the study and there will be no penalty. If your child initially agrees to be in the study they can change their mind later without any penalty.

Will there be any compensation?

Your child will receive a $5 gift certificate from Target as compensation for their participation in this study. Payments will occur after completion of neuropsychological tasks and questionnaires. You will be responsible for any taxes assessed on the compensation. If your child decides to withdraw from the study, they will still receive the compensation.

How will your child's privacy and confidentiality be protected if s/he participates in this research study?

Your child's privacy and the confidentiality of his/her data will be protected by by randomly assigning them a number (ranging from 001 to 100) at the outset of the study. All completed forms will be de-identified. A roster of individual names and their corresponding participant numbers will be maintained in a separate, locked filing cabinet from the participant forms. Their privacy will be protected by providing a private place for them to complete neuropsychological tasks.

If it becomes necessary for the Institutional Review Board to review the study records, information that can be linked to your child will be protected to the extent permitted by law. Your child's research records will not be released without your consent unless required by law or a court order. The data resulting from your child's participation may be made available to other researchers in the future for research purposes not detailed within this consent form. In these cases, the data will contain no identifying information that could associate it with your child, or with your child's participation in any study.

Participants will be given notice at least twenty-four hours prior to a researcher's arrival at their homes or other non-public places where they will be tested. Researchers will not show up unannounced. If the researcher(s) observe or otherwise learn of child or elder abuse while visiting your home, confidentiality will be broken: state law requires the reporting of abuse to relevant agencies. If I should observe or otherwise learn of child or elder abuse while visiting the participant's home, confidentiality will be broken. The researcher will report the abuse to relevant agencies (Child Protective Services or the Texas Department of Family and Protective Services) as required by law.

Whom to contact with questions about the study?

Prior, during or after your participation you can contact the researcher Thea Norris at (405) 742-4389 or send an email to thea.norris@utexas.edu for any questions or if you feel that you have been harmed.

This study has been reviewed and approved by The University Institutional Review Board and the study number is 2014-04-0112.

Whom to contact with questions concerning your rights as a research participant?

For questions about your rights or any dissatisfaction with any part of this study, you can contact, anonymously if you wish, the Institutional Review Board by phone at (512) 471-8871 or email at orsc@uts.cc.utexas.edu.

Signature

You are making a decision about allowing your child to participate in this study. Your signature below indicates that you have read the information provided above and have decided to allow them to participate in the study. If you later decide that you wish to withdraw your permission for your child to participate in the study you may discontinue his or her participation at any time. You will be given a copy of this document.

_____
Printed Name of Child

_____ _____
Signature of Parent(s) or Legal Guardian Date

_____ _____
Signature of Investigator Date

Appendix C: Assent Form

Assent for Participation in Research

Title: Family Functioning as a Moderator of Neurocognitive Outcome Among Survivors of Pediatric Acute Lymphoblastic Leukemia

Introduction

You have been asked to be in a research study about families and how people pay attention and think. This study was explained to your parent and they said that you could be in it if you want to. We are doing this study to learn about ways to help children who have survived cancer think and learn better.

What am I going to be asked to do?

If you agree to be in this study, you will be asked to do some attention tasks. This study will take 90 minutes and there will be 60 other people in this study.

What are the risks involved in this study?

Minimal risk in participating in this study includes emotional distress from completing measures. If this occurs, emotional support will be provided by a licensed psychologist.

Another possible risk that all participants may incur by participating in this study is a loss of confidentiality if study measures were to be lost. This risk will be addressed by: (i) use of subject numbers only to label any study materials and (ii) storage of all completed measures in a designated locked cabinet separate from the roster that links subject numbers with names of participants.

Any incident that occurs that in any way compromises the rights or welfare of the participants will be reported by the principal investigator to the Institutional Review Board within five days of its occurrence as an unanticipated event, per board policy.

If I should observe or otherwise learn of child or elder abuse while visiting the participant's home, confidentiality will be broken. The researcher will report the abuse to relevant agencies (Child Protective Services or the Texas Department of Family and Protective Services) as required by law.

Do I have to participate?

No, participation is voluntary. You should only be in the study if you want to. You can even decide you want to be in the study now, and change your mind later. No one will be upset.

If you would like to participate sign below and give this form back to the researcher. You will receive a copy of this form so if you want to you can look at it later.

Will I get anything to participate?

You will receive a $5 gift certificate from Target for participating in this study. Payments will occur after you have completed your attention tasks. If you decide to withdraw from the study, you will still receive the payment.

Who will know about my participation in this research study?

The records of this study will be kept private. Your responses may be used for a future study by these researchers or other researchers.

Whom to contact with questions about the study?

Prior, during or after your participation contact the researcher Thea Norris at (405) 742-4389 or send an email to thea.norris@utexas.edu for any questions or if you feel that you have been harmed.

Signature

Writing your name on this page means that the page was read by or to you and that you agree to be in the study. If you have any questions before, after or during the study, ask the person in charge. If you decide to quit the study, all you have to do is tell the person in charge.

_____ _____

Signature of Participant Date

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